Improving outcomes through statin therapy – a review of ongoing trials

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Statin treatment reduces cardiovascular risk in a wide variety of patients. Ongoing studies seek to define better the full range of benefits of such treatment. The issue of how far low-density lipoprotein cholesterol should be lowered for optimal reduction of coronary heart disease risk is being assessed in the TNT, IDEAL and SEARCH trials. The relationships among statin treatment, cardiovascular outcomes and levels of the inflammatory marker C-reactive protein are being assessed in the PROVE-IT and JUPITER trials. Mechanisms for the effects of statin treatment in preventing recurrent events when given early after occurrence of acute coronary syndromes are being examined in the LUNAR trial. The potential benefits of statin therapy in the setting of chronic heart failure are being evaluated in the CORONA, GISSI-HF and UNIVERSE trials. The results of these trials will provide important information on how to maximise the therapeutic benefits of statins in a broader range of patients at risk for cardiovascular morbidity and mortality.

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Introduction

Statin therapy is well established as an effective means for reducing risk of coronary heart disease (CHD).1-6 This evidence base has recently been expanded, with the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial7 showing benefits in elderly patients, a subgroup analysis of the Heart Protection Study demonstrating significant CHD risk reduction in patients with diabetes8 and the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA)9 showing benefits in patients with treated hypertension. A number of questions regarding use of statins to prevent cardiovascular disease remain to be answered, however. What is the optimum level of low-density lipoprotein cholesterol (LDL-C) to prevent cardiovascular disease? Can statin therapy modify the role of inflammation in the atherosclerotic process? By what means does early initiation of statin therapy reduce recurrence of events in patients with acute coronary syndromes? Can statin therapy improve survival in patients with chronic heart failure (CHF)? A number of ongoing studies in these areas will provide answers to these questions and should help physicians make evidence-based decisions as they seek to treat the wider patient population at risk for CHD.

How low should we go in reducing low-density lipoprotein cholesterol?

It has become commonplace to cite the linear relationship between LDL-C achieved on treatment and CHD event rates in statin studies as evidence that additional reductions in LDL-C would provide proportionate risk reduction.10 The finding in the Heart Protection Study6 that an identical degree of risk reduction was observed in patients irrespective of initial LDL-C levels, including those with levels below current targets, has served to...
Atherosclerosis is an inflammatory disease. A number of currently used Framingham risk algorithm and that it levels, that it adds prognostic information to the current risk, that it identifies at-risk individuals with low LDL-C levels, that it strengthens predictor of cardiovascular events than LDL-C, and that results of this event-driven trial will become available in 2004 or 2005.

The Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) trial was also designed to evaluate the effects of aggressive lipid-lowering therapy on CHD events in patients with existing CHD. A total of 8888 patients aged ≤ 80 years with a history of myocardial infarction (MI) have been randomised to aggressive treatment with atorvastatin 80 mg or ‘conventional’ treatment with simvastatin 20–40 mg. The trial is designed to have a 5-year follow-up but is event driven, and it is likely that enough events will have accrued to permit reporting of findings in 2005.

The Study of the Effectiveness of Additional Reduction in Cholesterol and Homocysteine (SEARCH) trial is comparing the effects of simvastatin 20 mg vs simvastatin 80 mg in 12,000 patients with prior MI. In addition, the trial is examining the effects of reducing homocysteine levels with folic acid treatment. Scheduled follow-up in this trial is 5 years, and reporting of results is expected in 2004 or 2005.

Can statin therapy modify the role of inflammation in the atherosclerotic process?

Atherosclerosis is an inflammatory disease. A number of markers of systemic inflammation have been found to correlate with cardiovascular risk. Principal among these, due to its predictive power and clinical usefulness, is C-reactive protein (CRP). CRP level is associated with increased risk of peripheral vascular disease, MI, stroke and sudden cardiovascular death. It has been reported that a single measurement of CRP is a stronger predictor of cardiovascular events than LDL-C, that it identifies at-risk individuals with low LDL-C levels, that it adds prognostic information to the currently used Framingham risk algorithm and that it identifies high risk for cardiovascular events in individuals with the metabolic syndrome. Statin treatment has been found to reduce CRP levels; this effect, which appears to be dose related, may be due to reduced LDL oxidation (as a consequence of lowered LDL particle number) and/or additional anti-inflammatory activities that statins exert independently of the decrease in LDL.

Patients with high baseline CRP have been found to derive marked benefits from statin therapy, and there is some evidence that larger reductions in CRP may translate into greater anti-atherosclerotic effects. Analysis of findings in the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) trial in familial hypercholesterolaemia, for example, showed that aggressive dosing of atorvastatin at 80 mg reduced CRP more than ‘conventional’ dosing with simvastatin 40 mg (40% vs 20% at 2 years) and that reduction of CRP was correlated with reduction of carotid intima-media thickness on univariate analysis.

Ongoing trials are assessing the relationship among statin treatment, effects on CRP, and cardiovascular outcomes. The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial is comparing the effects of aggressive treatment with atorvastatin 80 mg, with a target LDL-C of 1.8 mmol/l (70 mg/dl), against pravastatin 40 mg, with a target LDL-C of 2.6 mmol/l (100 mg/dl). Pravastatin has been reported to have marked beneficial pleiotropic effects on the vasculature that are independent of cholesterol reduction, and this trial will assess whether the magnitude of preventive benefit with pravastatin treatment is comparable to that with atorvastatin despite the predicted lesser reduction in LDL-C. A total of 4160 patients presenting within 10 days after hospitalisation for acute MI or high-risk angina with total cholesterol ≤ 6.2 mmol/l (240 mg/dl) have been enrolled. Patients are being followed for 2 years (minimum of 18 months) to determine rates of hospitalisation for unstable angina, revascularisation at ≥ 30 days after enrollment, MI, stroke and death. To explore the potential contribution of microbial infection and related inflammation to atherosclerosis, this trial is also assessing the effectiveness of anti-Chlamydia pneumoniae treatment with gatifloxacin in reducing cardiovascular risk. Results of this trial are expected to be available soon.

The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was designed to assess the effectiveness of rosuvastatin in the primary prevention of cardiovascular events in individuals with normal LDL-C levels and elevated CRP levels. A target of 15,000 patients (men aged >55 years and women aged >65 years) with no history of coronary disease, LDL-C < 3.4 mmol/l (130 mg/dl) and CRP levels ≥ 2.0 mg/dl are to be randomised to rosuvastatin 20 mg or placebo (Fig. 1). The use of placebo will be permitted in this trial because these individuals are not candidates for lipid-lowering therapy according to current guidelines. The CRP entry criterion of ≥ 2.0 mg/l for this trial is lower than the 3.0 mg/l cut point recently suggested to define elevated risk. Patients will undergo periodic lipid and CRP measurements and will be followed for unstable angina, revascularisation, MI, stroke and cardiovascular death. The trial is
Can early institution of statin therapy reduce recurrence in acute coronary syndrome patients?

The Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study assessed the effectiveness of atorvastatin 80 mg vs placebo given at 24–96 h after hospitalisation in preventing recurrent events in 3086 patients with acute coronary syndrome (unstable angina or non-Q-wave acute MI). The primary end point (recurrent symptomatic ischaemia with objective evidence and requiring emergency rehospitalisation, cardiac arrest with resuscitation, non-fatal MI or death) occurred in 14.8% of atorvastatin patients and 17.4% of placebo patients (relative risk, 0.84; 95% confidence interval [CI], 0.70–1.00) over 16 weeks. There were no significant differences between the atorvastatin and placebo groups with regard to cardiac arrest, non-fatal MI or death, although the atorvastatin group had lower risk of the symptomatic ischaemia component of the composite end point (6.2% vs 8.4%; relative risk, 0.74; 95% CI, 0.57–0.95). There were no significant differences between the two groups with regard to the secondary outcomes of revascularisation, worsening heart failure or worsening angina, but there was a reduced frequency of stroke in the atorvastatin group (12 vs 14 events, $P = 0.045$). These findings suggest that there may be benefit in early statin treatment in patients with acute coronary syndromes.

The Limiting Undertreatment of Lipids in ACS with Rosuvastatin (LUNAR) trial was designed to investigate the mechanism of potential benefits of early statin therapy in the setting of acute coronary syndromes. Patients are being randomised to open-label treatment with rosvastatin 20 or 40 mg or atorvastatin 80 mg for 12 weeks. Lipid changes and pleiotropic effects are being measured to help determine what effects of statin treatment might play a role in preventing recurrent events.

Can statin therapy improve survival in patients with heart failure?

Statins appear to exert effects that reduce inflammation and improve endothelial function, activities that may be of benefit in patients with CHF. The potential role of statin therapy in CHF is being examined in a number of trials. CORONA (the Controlled ROsvastatin Multi-national Trial in Heart Failure) is a long-term (approximately 5 year) randomised, double-blind, placebo-controlled, multi-national study evaluating the effects of low-dose rosvastatin in CHF. Patients aged ≥60 years with chronic symptomatic systolic HF (ejection fraction ≤0.35 for New York Heart Association class II disease or ≤0.40 for class III/IV disease) of ischaemic etiology who are receiving standard treatment excluding lipid-lowering therapy have been randomised to receive rosvastatin 10 mg or placebo and are being followed for cardiovascular events and survival. The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico-Heart Failure (GISSI-HF) trial is an Italian study comparing the effects of rosvastatin and fish oil on cardiovascular morbidity and mortality in patients with CHF of any etiology. The Rosuvastatin Impact on Ventricular Remodelling Lipids and Cytokines (UNIVERSE) trial is an Australian study assessing the effects of rosvastatin on cardiac remodeling in HF patients.

Conclusion

Statin therapy has been shown to reduce cardiovascular risk in a wide range of patients. Additional investigations are needed to define better the full range of benefits and potential uses of such therapy. Ongoing trials will provide answers to the questions of how low LDL-C should be reduced to maximise preventive benefit, whether statin...
treatment can reduce risk of clinically overt disease by virtue of anti-inflammatory effects, how statin treatment can affect short-term outcome of acute coronary syndromes and whether statin treatment can influence the course of CHF. The findings from these studies should guide clinicians to more effective use of these agents in a greater variety of patients.

References