

Statins: targeting cardiovascular disease

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ABSTRACT The explosion of medical knowledge and the importance and real reductions in adverse cardiovascular events with improving medical therapy has seen a surge in large trials investigating the use of HMG-CoA reductase inhibitors (statins) in the treatment of patients with cardiovascular disease since the 1990s. The established pathological role of low density lipoprotein (LDL) cholesterol and the efficacy of the lipid lowering properties of statins have ushered in an effective means of managing and preventing major adverse cardiovascular events (MACE). The purpose of this article is to review the evidence to date illustrating the benefits of statin therapy and highlight some of the key features of the landmark trials in order to gain more insight in their use in the acute coronary syndromes. SAHeart 2008; 5:66-69

THE ORIGINAL OR LANDMARK STUDIES

Initially the landmark statin trials proved the benefit of using HMG CoA reductase inhibitors or "statins" in the hypercholesterolemic patient with heart disease. The Scandinavian Simvastatin Survival Study (4S) was such a secondary prevention study in which patients with angina or prior myocardial infarction with elevated cholesterol were randomized to receive either simvastatin or placebo and followed over a median of 5.4 years. There was a significant reduction in MACE rates as well as a reduction in the need for further coronary revascularization.⁽¹⁾

Following on the success of this secondary prevention trial, major primary prevention trials which examined the role of statins in hypercholesterolemic men without a prior history of myocardial infarction were reported. The West of Scotland Primary Prevention Study (WOSCOPS) demonstrated a 31% reduction in non-fatal myocardial infarction or coronary deaths, a 37% reduction in revascularization procedures and overall a 32% reduction in cardiovascular mortality.⁽²⁾

The Long Term Intervention with Pravastatin in Ischemic Disease (LIPID) study emphasized the importance of statins in secondary prevention by reducing mortality across a wide range of serum cholesterol levels (4-7 mmol/L) in long-term (mean 6.1 years) treatment. The benefit was mostly shown in patients with high cholesterol levels at baseline.⁽³⁾

The Cholesterol and Recurrent Events (CARE) study published reductions in coronary events by 24% in patients with prior history of cardiovascular disease but with average cholesterol levels (5.4 +/- 0.4 mmol/L).⁽⁴⁾

Most of these trials failed to show reductions in non-cardiovascular events.

One of the largest statin trials to date, the Heart Protection Study (HPS) demonstrated significant reductions in MACE, strokes and in revascularization procedures regardless of initial LDL levels.⁽⁵⁾ Total mortality was reduced significantly (RR 0.87, 95%CI 0.81-0.91, p=0.0003). The benefit was clearly seen in the elderly, in a high risk population, in female patients, diabetics and in patients with non-cardiac atheromatous disease. In fact there was a proportional reduction in adverse events in all categories of lipid levels, even those with low LDL levels.

Reductions in MACE with statin use as primary prevention in an average risk population with normal total cholesterol (5.7 +/- 0.54 mmol/L) but with low HDL (<0.16 mmol/L for men and <1.22 mmol/L for women) was also demonstrated in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS).⁽⁶⁾

TREATMENT IMMEDIATELY AFTER ACUTE CORONARY SYNDROMES

As statins gained popularity, further research began to explore their potential pleiotropic effects. Statins can modify endothelial function, stabilize plaques, reduce inflammation and prevent thrombus formation. It seemed logical that the next step would be to use them early in the setting of the acute coronary syndromes.

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, high dose (80mg daily) atorvastatin used early (within 24-96 hours) in non-Q wave myocardial infarction and unstable angina demonstrated a mean reduction in total cholesterol of 34% and significant reduction in recurrent unstable angina (26%) but no significant change in death, non-fatal myocardial infarction or cardiac arrest at 16 weeks follow-up.⁽⁷⁾ This was a randomized, placebo-controlled trial and demonstrated a reduction in composite cardiovascular events by 16% ($p=0.048$) over the ensuing 4 months. Perhaps even more striking was the 50% reduction in stroke achieved in this study.

The Atorvastatin Versus Revascularization Treatment (AVERT) study compared aggressive atorvastatin therapy to coronary angioplasty. Although risk reduction was not significant after adjustment for interim analysis, the time to reach an ischemic event was significantly longer in the atorvastatin group (RR 0.64, 0.33-0.95, $p=0.03$).⁽⁸⁾

MORE AGGRESSIVE TREATMENT

Since higher doses of statins are able to lower lipid levels more significantly, especially in the acute setting, questions arose as to whether high dose statin therapy, particularly with the use of the more potent statins, may lower event rates more than standard dose therapy.

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT) trial, patients were randomized to standard therapy or intensive therapy 10 days after an episode of acute coronary syndrome.⁽⁹⁾ The primary end-point was the composite of death, myocardial infarction, hospitalized unstable angina, revascularization and stroke. At the end of two years, the primary end point rate was 26.3% with standard therapy and 22.4% with intensive therapy. Progressively lower risk with progressively lower achieved LDL-cholesterol levels was achieved even in those patients with relatively low initial LDL-cholesterol levels.

A similar reduction in the composite primary end-point was observed in the A to Z trial.⁽¹⁰⁾ This occurred more significantly when early intensive therapy where high dose statin (simvastatin 80 mg daily) was initiated within 5 days of presenting with acute coronary syndrome than with delayed conservative therapy where lower dose statin was given 4 months after presentation.

In the Treating to New Targets (TNT) study, patients with stable coronary artery disease who achieved LDL levels after an 8-week run-in period on low dose atorvastatin were randomized to either 10mg or 80mg atorvastatin daily. The mean LDL-cholesterol levels obtained were 2.6 mmol/l on the 10mg dose compared to 2.0 mmol/l on the 80mg dose of atorvastatin. A 22% reduction in cardiac events following a mean follow-up period of 5 years was seen with intensive therapy but overall mortality was not significantly different.⁽¹¹⁾

In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL), luminal stenosis measured on intravascular ultrasound was shown to be significantly increased after 18 months in patients 30-75 years old with moderate lipid therapy compared with intensive therapy.⁽¹²⁾

In the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) study, patients were randomized to either 20mg or 80mg of atorvastatin daily.⁽¹³⁾ Patients selected were those with a prior history of myocardial infarction and most were therefore already on a statin. The primary endpoint of the trial was time to first occurrence of coronary death, myocardial infarction or resuscitated cardiac arrest over a 5-year period. An 11% significant reduction in the primary endpoint occurred with intensive therapy.

A meta-analysis of the A to Z, IDEAL, PROVE-IT and TNT studies compared intensive versus moderate statin therapy.⁽¹⁴⁾ This showed a 16% ($p<0.0001$) reduction in coronary death or myocardial infarction, and an 18% reduction in stroke, ($p=0.012$), but little effect on cardiovascular death ($P=0.73$).

In composite, these randomized trials and meta-analyses indicate that benefits of statins are apparent within 4 months after acute coronary syndromes manifested, primarily as a reduction in recurrent unstable angina. Also, higher intensity statin treatment affords greater benefit than lower intensity treatment in both early and later timeframes after acute coronary syndromes.

THE SAFETY OF STATINS

With such successful results garnering in an era of widespread statin use and evidence of more beneficial effects with higher doses, safety concerns undoubtedly develop. Cholesterol is a core component of cellular membranes and lowering levels intensively could interfere with normal regenerative processes. Ophthalmopathy and encephalopathy occurred in early studies with dogs on very high doses. However, this has not been demonstrated to occur in man.

Statins are remarkably safe and well-tolerated drugs.^(15,16) Even at high doses the major adverse effects of the statins, namely myopathy and raised liver enzymes, are uncommon. The risk of rhabdomyolysis is < 4 per 100 000 patient years.

The normal LDL-cholesterol range is 1 – 1.8 mmol/l in healthy neonates, hunter-gatherers and free living primates.⁽¹⁷⁾ Randomized clinical trials comparing intensive to moderate LDL-cholesterol reduction with statin therapy suggest that coronary events are minimized when the LDL-cholesterol is lowered to below 1.8 mmol/l. However, this still needs to be confirmed in prospective randomized trials. No major safety issues have occurred in studies such as the ARBITER and ASTEROID in which LDL-cholesterol levels were reduced to below 1.8 mmol/l with no adverse effects.⁽¹⁸⁾

CONCLUSION

Statin therapy for primary and secondary prevention of cardiovascular disease has become firmly established, and the use of statins in patients with, or at high risk for cardiovascular disease represents a major advance in pharmacotherapy for the prevention and treatment of cardiovascular events. Liberal use of the drugs has made statins arguably the most extensively prescribed medications worldwide and relevant usage clearly has improved options for these patients. The astute clinician needs to be mindful of the rare side effects and individual surveillance is mandatory. New evidence suggests that intensive lipid-lowering with high doses of the more potent statins results in lower event rates than moderate lipid lowering and the greatest benefits are related to the greatest reductions in LDL-cholesterol.⁽¹⁴⁾ However, how “low to go” remains unanswered. Although none of the abovementioned trials targeted a specific level of cholesterol, all of them demonstrated significant reduction of LDL-cholesterol levels. Notably, the ASTEROID trial demonstrated a significant reduction in atheroma burden on IVUS examination after 75% of patients achieved a mean LDL-C level of 1.8mmol/L during treatment with aggressive rosuvastatin therapy.⁽¹⁸⁾

Statin therapy should now be considered routine in all patients following an acute coronary event. Follow-up testing of LDL cholesterol levels should be mandatory to monitor effectiveness of individual drug use and assess adherence to therapy and dietary advice. However, in South Africa, as in most countries, despite the documented benefit of early intensive statin therapy post an acute coronary event, there appears to be a reluctance to prescribe statin therapy, particularly high-dose statin therapy. All physicians should try to adhere to the latest South African Lipid guidelines, which have been adopted from the European guidelines and should be encouraged to prescribe these remarkable drugs in patients at high risk or with documented cardiovascular disease.⁽¹⁹⁾ They should strive to achieve the LDL-cholesterol goal of < 2.5 mmol/l in all patients with established coronary artery disease.

Coronary artery disease in the HIV-positive population, particularly those receiving highly active anti-retroviral therapy, needs further investigation considering our local situation. The dyslipidemic effects of anti-retroviral therapy as well as the endothelial dysfunction induced by the virus itself are alarming. Further study and monitoring in the South African setting is paramount.

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