Clinical Opinion

J R Coll Physicians Edinb 2005; **35:**110–111

High-dose statin therapy in patients with coronary artery disease

TG Trouton
Consultant Cardiologist, Antrim Area Hospital Antrim, Northern Ireland

TITLE Intensive vs moderate lipid lowering with statins after acute coronary syndromes

AUTHORS Cannon CP, Braunwald E, McCabe CH *et al.*

JOURNAL *N Engl J Med* 2004; **350:**1495–504

KEYWORDS Coronary artery disease, statin

LIST OF ABBREVIATIONS High density lipid (HDL), low density lipid (LDL), myocardial infarction (MI), Scandinavian Simvastatin Survival Study (4S), total cholesterol (TC)

DECLARATION OF INTERESTS No conflict of interests declared.

***Correspondence to* TG Trouton, Consultant Cardiologist, Antrim Area Hospital, Bush Road, Antrim, Northern Ireland, BT41 2RL**

***tel.* +44 (0)28 9442 4287**

***fax.* +44 (0)28 9442 4679**

***e-mail* Tom.Trouton@uh.n-i.nhs.uk**

SUMMARY

There has been much interest in the statin group of drugs over the last 15 years in patients with coronary artery disease, particularly since clinical outcomes were demonstrated to improve in the the 4S study in patients treated with simvastatin vs placebo. The current randomised controlled trial in lipid-lowering strategies was a head-to-head comparison of two major protagonists in the lipid-lowering field at present, pravastatin and atorvastatin. The aim was to establish non-inferiority of standard therapy (40 mg pravastatin) with intensive therapy (80 mg atorvastatin). The study design was a simple two-way randomisation and the study population was patients hospitalised with an acute coronary syndrome.

Four thousand one hundred and sixty-two patients were enrolled in the study and were followed for a mean of 24 months. Patients treated with 80 mg atorvastatin achieved a significantly lower LDL level than those given 40 mg pravastatin (1·60 mmol/l vs 2·46 mmol/l). There was also a significant difference in the reduction in clinical endpoints (death from any cause, MI, unstable angina requiring hospitalisation, revascularisation and stroke) between pravastatin (26·3% of patients) and atorvastatin (22·4%) at two years.

The investigators conclude that patients with established coronary disease benefit from early and continued lowering of LDL-cholesterol to levels substantially below current target levels.

OPINION

It is a closely guarded secret that no cardiologist has looked at a lipid profile since the turn of the century. We exercise our knowledge of triglycerides, HDL-cholesterol etc. to appear polite in mixed company. In the last decade we have witnessed the remarkable outcomes of aggressive lipid lowering (mostly with statins) both in the catheterisation laboratory and the clinic, have stealthily cleared our shelves of European, national, regional and local lipid guidelines and continued on our quest to statin-ise the atherosclerotic population using moderate to high doses of the statins available to us. The above trial vindicates our practice but, as any good study should do, provokes further questions about future use of these drugs and the management of these patients.

A sexed-up relative risk reduction of 16% hides a more modest sounding absolute (yet significant) risk reduction between the two drugs of 3·9% for the pre-determined combined endpoint. Although modest, this is probably very important given that we are comparing two commonly used drugs within the same class. Also, considering the endpoint is death, MI, revascularisation etc., one has to ask which drug one would take oneself under the circumstances.

In this study approximately 22% of patients in both groups had stopped their trial drug by 12 months, rising to 33% by 24 months. Having probably prescribed or advised more statins in higher doses than ever before in the last 12 months, I have also cancelled more. This has been due to an undoubted intolerance of these higher doses. Subtle symptoms of muscle aches, rashes, joint pains,

bloating, dyspepsia and mood changes have all been cited to me by an informed patient population. I fear that fewer of our eligible patients will be able to take these high statin doses long-term.

What about my average patient with a 'mixed' picture on the lipid profile of elevated triglycerides and low HDL-cholesterol? These outcasts never made it to the majority of lipid trials of the 1990s, yet the conclusions were extrapolated by the back door of subgroup analysis after the event. We are entirely in the dark as regards adding in fibrates, nicotinic acid or ezetimibe to these high statin doses in the patients in whom the HDL remains low or the TC:HDL ratio or triglycerides remains high. This study probably includes such patients but they are not separately identifiable within the protocol or results. Neither efficacy nor side effects are known with high-dose combination therapies and more trials will be required to clarify this area.

It is clear from this study that there is now no logic in assuming a minimum cholesterol target in patients with established coronary atherosclerosis. The clear message from this study regarding secondary prevention and hyperlipidaemia is that we could do better. For cardiologists the time has come to start crunching the numbers again.