

Statin therapy following percutaneous coronary revascularisation: time to make LIPS stick?

The success of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) in ameliorating atherothrombotic events is firmly established. Large randomised controlled clinical trials have consistently (and unequivocally) demonstrated a beneficial role in reducing coronary events and total mortality in patients with advanced coronary artery disease (CAD).^{1,2} The benefits extend to primary prevention.³⁻⁵ This success has led investigators to explore mechanisms and to study the role of statins in different patient populations.

The Lescol Intervention Prevention Study (LIPS) falls into the latter category.^{6,7} Percutaneous coronary intervention (PCI) is effective at providing relief from angina in patients with flow-restricting coronary atheroma. The rationale for the study arose from observations that, in spite of symptom palliation, patients continue to have high rates of adverse events after the procedure. Approximately 60% of patients at five years and only 33% at 10 years remain free of major cardiac events.⁸ Lipid-rich plaques are vulnerable to rupture. Some may not cause luminal narrowing and these are difficult to diagnose by coronary angiography.⁹ There is a need, therefore, for measures to stabilise plaques in conjunction with lowering cholesterol.

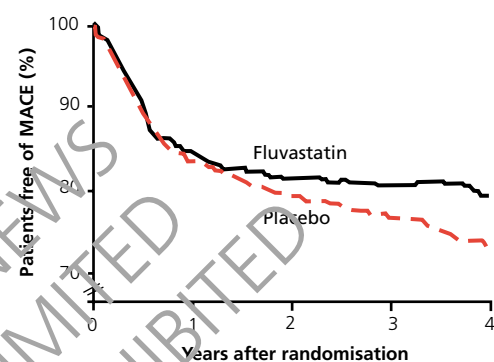
The LIPS study

LIPS was a double-blind, randomised, placebo-controlled trial to investigate whether cholesterol lowering initiated within days of successful PCI would prolong freedom from cardiac events. The study design took account of the Fluvastatin Angioplasty Restenosis (FLARE) study¹⁰ that showed no effect on restenosis after six months of fluvastatin treatment. Therefore, the end point in LIPS was assessed in a pre-specified analysis excluding re-interventions in the first six months for lesions treated at the index PCI procedure.

LIPS recruited 1,677 patients (during 1996–1998) undergoing their first PCI in native coronary artery. Baseline characteristics differed only in an excess of patients with diabetes in the fluvastatin group (14.2% vs. 9.8%). Therapy was initiated at a median of two days after PCI. Enrolment stipulated patients must have a total cholesterol level between 3.5–7.0 mmol/L with a fasting triglyceride level of < 4.5 mmol/L.

At the time of the study design, this was a radical depart-

Figure 1. Results of the LIPS study comparing the effect of fluvastatin on major adverse cardiac events post-percutaneous coronary intervention



Number at risk	0	1	2	3	4
Fluvastatin	844	703	666	647	250
Placebo	833	686	642	610	228

Key: MACE = major adverse cardiac events; $p=0.01$ by log-rank test

Adapted from Serruys PW *et al.*⁶

ture from earlier trials^{1,3,11} since it included patients with average (for industrialised nations) cholesterol levels. Hitherto, published trials had only included patients with some manifestation of CAD and/or high cholesterol level. Patients were randomly assigned to placebo or fluvastatin (Lescol®, Novartis Pharma AG, Switzerland) 40 mg b.d. for between three and four years. The primary end point was development of major adverse cardiac events (MACE), defined as cardiac death, non-fatal myocardial infarction (MI) or coronary revascularisation.

In previous statin intervention studies, only 8–30% of patients had undergone PCI and therapy was initiated at least six months after intervention. The LIPS study, although a variation on secondary prevention, is unique in being a prospective trial of patients undergoing their first PCI with clinical outcomes as the primary end point. Furthermore, the major difference between the design of LIPS and studies published at the time (1996) was the inclusion of patients with average cholesterol levels.

Results revealed MACE-free survival to be significantly longer in the fluvastatin group (figure 1). The Kaplan-Meier

curve separated at 30 months and continued to diverge to study end.

Subgroup analysis revealed lower risk of MACE in the fluvastatin group for patients with multivessel disease and patients with diabetes. MACE rates were similar in the fluvastatin arm (20.9%) dichotomised on the basis of cholesterol level above or below the group median (5.2 mmol/L). For placebo, the respective figures were 27.5% and 25.3%.

Implications

Statins are singularly effective at reducing MACE in patients with advanced CAD and elevated cholesterol level. This study advances our knowledge in demonstrating benefit to patients with relatively minor CAD and average cholesterol levels.

This finding alone is likely to have profound implications for clinical practice. It begs the question "Is there a level of cholesterol below which statins are either ineffective or not cost effective?" Elevated cholesterol level is an established independent risk factor for development of cardiovascular disease. However, the value of cholesterol and the optimal time for initiation of therapy in patients with normal or low low-density lipoprotein (LDL) cholesterol levels (< 3.4 mmol/L) are contentious.

Both the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) and Cholesterol And Recurrent Events (CARE) studies^{2,11} suggest benefit is diminished in patients with an LDL cholesterol < 3.4 mmol/L at initiation. By contrast, LIPS and the Heart Protection Study⁵ suggest benefit to be significant and equal regardless of baseline values. The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults recommended reduction of LDL cholesterol to < 2.6 mmol/L in patients with CAD.¹² This advice would appear to sit comfortably with mechanistic explanations of benefit from statins resulting in plaque stabilisation. These benefits arise not only from effects on atherogenic lipoproteins but equally from their pleiotropic effects on inflammation,¹³ endothelial function,¹⁴ myocardial protection¹⁵ and thrombogenesis.¹⁶

For clinicians involved in the management of patients suitable for revascularisation, LIPS data support the view that, with established CAD, statins should be initiated regardless of cholesterol level. These patients should be commenced on lifelong therapy together with advice for lifestyle and dietary modifications. This recommendation can be made with the knowledge that all statin studies involving large numbers of patients have shown a good safety profile. The high crossover rate from placebo to active medication in LIPS, favourable results across subgroups coupled with results from other trials have set the seal on future studies. No longer is it ethical to compare statins against placebo in patients with CAD. Future trials will need to compare different statin drugs or different

dosage regimes of the same drug. Alternatively, they will explore the effects on different clinical scenarios such as acute coronary syndromes.

Finally, early statin studies enrolled patients with advanced CAD. Modern cardiology practice in the UK is changing, albeit slowly. Investigational facilities for early detection of CAD are increasing and the PCI patient profile is evolving from the patient with chronic angina to one presenting with a first episode of angina. This gives clinicians an opportunity, supported by data from LIPS, to address early, both the metabolic and mechanical components of CAD, thereby favourably altering its natural history and progression. This fact alone is a welcome legacy of the LIPS study and should persuade cardiologists to make LIPS stick.

Conflict of interest

None declared.

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