CARDIOVASCULAR DISEASE

Intensive care

Are all statins created equal? Invariably not is the answer, but this has been based largely on extrapolating data from several placebo-controlled trials. Now, the first two head-to-head statin studies agree that the more intensive LDL-cholesterol-lowering effects of atorvastatin (Lipitor; Pfizer) provide superior surrogate and clinical benefits to the moderate effects of pravastatin (Pravachol; Bristol-Myers Squibb).

In the Pfizer-funded REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial, published in the *Journal of the American Medical Association*, Steven Nissen and colleagues examined the progression of atherosclerosis in 502 patients with stable coronary disease, randomly assigned to a moderate lipid-lowering regimen of 40 mg per day pravastatin or an intensive regimen of 80 mg per day atorvastatin during an 18-month period. The pravastatin dose was selected because it was the highest approved dose at the time of study initiation and was one of the best-studied regimens in secondary prevention of coronary events. The atorvastatin dose was selected because it produced the largest reduction in atherogenic lipoproteins of any available therapy at that time.

As expected, LDL cholesterol levels were reduced more in the atorvastatin group. Using a novel technique called intravascular ultrasound (IVUS), which produces detailed images of a vessel wall, the researchers found that atorvastatin also halted the growth of lipid plaques that lead to atherosclerosis (–0.4% progression rate). By contrast, atherosclerosis still progressed with pravastatin (2.7%).

How this could translate into clinical effects is revealed by the Bristol-Myers Squibb-funded PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial. In this non-inferiority study, published in the *New England Journal of Medicine*, Cannon, Braunwald and colleagues compared the clinical effects of the same doses of pravastatin and atorvastatin as REVERSAL over an average of 24 months in 4,162 patients with acute coronary syndromes. The risk of coronary events, such as mortality, myocardial infarction and unstable angina, was 26.3% for pravastatin and 22.4% for atorvastatin — representing a 16% risk reduction favouring atorvastatin. Given previous results from placebo-controlled trials in stable patients, in which event curves separated only after 12–24 months, such a rapidly evident difference in effect was unexpected.

One suspicion is that LDL-cholesterol lowering is not the only benefit of statins, and that anti-inflammatory effects might also have a role. Both REVERSAL and PROVE-IT showed a difference in anti-inflammatory effects, as atorvastatin produced a greater reduction in levels of the inflammatory marker C-reactive protein.

So, these studies convey many messages. First, their conclusions will change prevention of cardiovascular diseases. In general, current cholesterol-lowering guidelines are set around moderate statin regimens. Second, the observed clinical effects show that more patients should be treated with statins — although the higher cost of, and potential increased adverse risks with, aggressive statin therapies is likely to be an issue, as is whether these clinical effects will be observed in stable secondary prevention or primary prevention patients. Third, more company-funded, but independently conducted, head-to-head statin trials should be encouraged, to improve patient care. Last, the studies validate IVUS as a technique for monitoring the progression of atherosclerosis in blood vessels. IVUS and clinical events could therefore be used to investigate the full benefits of statins and other lipid-modifying therapies.

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References and links

ORIGINAL RESEARCH PAPERS Nissen, S. E. *et al.* Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* **291**, 1071–1080 (2004) | Cannon, C. P. *et al.* Comparison of intensive and moderate lipid lowering with statins following acute coronary syndrome. *N. Engl. J. Med.* 8 March 2004 (DOI: 10.1056/NEJMoa040583).