

Major journals

A major step forward in the treatment of coronary heart disease



Mark Kearney,
Cardiologist,
King's College
Hospital, London

In just 10 years, statins have become central to the management of atherosclerotic vascular disease. The first major statin trial – the Scandinavian Simvastatin Survival Study (4S) – provided definitive evidence that, compared with placebo, simvastatin improved survival.

Since then a number of large trials have confirmed these results in different patient groups. In 2002, the Heart Protection Study demonstrated that patients with 'normal' LDL cholesterol levels benefited from taking statins. During this time it has also emerged that statins may have beneficial effects above and beyond their effects on cholesterol, such as an anti-inflammatory effect supported by a reduction in C-reactive protein (CRP).

In a recent article published in the *New England Journal of Medicine*, Cannon et al compared the effects of 80 mg atorvastatin and 40 mg pravastatin on clinical outcomes in more than 4000 patients with acute coronary syndromes followed for a mean of 24 months.

The median LDL cholesterol achieved with pravastatin was 2.46 mmol/l compared with 1.6 mmol/l in patients receiving atorvastatin; CRP in the atorvastatin group was 1.3 mg/l compared with 2.1 mg/l in the pravastatin group. The primary endpoints of death, myocardial infarction, documented unstable angina requiring hospitalisation, revascularisation and stroke were 16% lower in the atorvastatin group.

The results of this study and of the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, also reviewed in this section, are a major step in the treatment of atherosclerosis. Previously it was considered optimal to lower LDL cholesterol to <2.6 mmol/l. In light of the work by Cannon et al and REVERSAL, our use of statins is likely to change. The results of Cannon et al demonstrate that the benefit achieved with aggressive statin use is similar to that seen in previous trials of statin vs placebo.

This study allied to REVERSAL represents a major step forward in the treatment of coronary artery disease. Treatment with statins monitored by CRP and LDL may be a new approach to improving outcome in this huge patient group.

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION



Atorvastatin halts progression of atherosclerosis

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓✓

1 The optimal statin strategy and target lipid levels in patients with coronary heart disease (CHD) remain uncertain.

2 This study (the REVERSAL trial), measured atherosclerosis progression in patients treated with two different statins over 18 months.

3 A total of 502 patients were randomised to receive either a moderate lipid-lowering regimen (40 mg pravastatin) or an intensive

regimen (80 mg atorvastatin).

4 Progression of atherosclerosis (% change in atheroma volume) was measured by intravascular ultrasound.

5 Change in atheroma volume was positive in the pravastatin group (2.7%) indicating progression of atherosclerosis, but negative in the atorvastatin group (-0.4%), indicating no disease progression.

6 Most atherogenic lipoproteins were reduced to a greater extent in the intensive treatment group.

7 These findings provide strong evidence that 80 mg atorvastatin (maximum approved dose) reduces atherosclerosis progression compared with a 40mg pravastatin (moderate regimen).

Nissen SE, Tuzcu EM, Schoenhagen P et al (2004) Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis. *Journal of the American Medical Association* **291**: 1071–80

NEW ENGLAND JOURNAL OF MEDICINE



More intensive lipid lowering increases clinical benefit

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 Statin therapy reduces the risk of cardiovascular events, but the target level for LDL cholesterol is unclear.

2 This randomised study compared the effects of 40 mg pravastatin (standard therapy) and 80 mg atorvastatin (intensive therapy), with the aim of establishing the non-inferiority of pravastatin with respect to time to endpoint.

3 The primary endpoint was a composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalisation, revascularisation (performed at least 30 days after randomisation) and stroke.

4 A total of 4162 patients hospitalised for an acute coronary syndrome within the preceding 10 days were enrolled in the study and followed up for a mean of 24 months (range 18–36 months).

5 Median LDL level during standard treatment was 2.46 mmol/l compared with 1.6 mmol/l during intensive therapy (P<0.001).

6 Rates of the primary endpoint at 2 years were 16% lower in the intensive therapy group (P=0.005).

7 The benefit of intensive therapy was consistent across prespecified subgroups, including those with and those without diabetes mellitus.

8 An intensive lipid-lowering regimen in patients with acute coronary syndrome provides greater protection against death or major cardiovascular events than does a standard regimen.

Cannon CP, Braunwald E, McCabe CH et al (2004) Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *New England Journal of Medicine* **350**(15): 1495–503

'This study assessed the value of CRP and other circulating inflammatory markers in the prediction of coronary heart disease'

NEW ENGLAND JOURNAL OF MEDICINE

How useful is C-reactive protein in predicting CHD?

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

- 1 Atherosclerosis is thought to be partly an inflammatory disease, hence C-reactive protein (CRP), an inflammatory marker, has been used to predict coronary events.
- 2 This study evaluated the value of CRP and other circulating inflammatory markers in the prediction of coronary heart disease (CHD).
- 3 CRP, erythrocyte sedimentation rate (ESR), and von Willebrand factor were measured in samples obtained at baseline from around 2400 patients who had a nonfatal myocardial infarction or died of CHD during the study, and from almost 4000 controls without CHD in the Reykjavik Study.
- 4 Long-term stability of CRP, ESR and von Willebrand factor values was similar to that for blood pressure and total serum cholesterol, suggesting that these markers are sufficiently stable for potential use in the long-term prediction of CHD.
- 5 After adjustment for established risk factors, the odds ratio for CHD was 1.45 in those in the top third of the group with respect to baseline CRP compared with those in the bottom third.

6 Odds ratios in the Reykjavik Study for CHD were weaker for ESR (1.30) and von Willebrand factor concentration (1.11), but stronger for established risk factors (2.35 for increased total cholesterol level; 1.87 for cigarette smoking).

7 It was concluded that CRP is a moderate predictor of CHD.

Danesh J, Wheeler JG, Hirschfield GM et al (2004) C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *New England Journal of Medicine* **350**(14): 1387–96

'It was suggested that CRP, ESR and von Willebrand factor values are sufficiently stable for potential use in the long-term prediction of coronary heart disease'

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Adiponectin levels and MI risk in men

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

- 1 Adiponectin is a recently discovered adipocyte-derived peptide involved in the regulation of insulin sensitivity and lipid oxidation.
- 2 This case-control study in 18 255 men from the Health Professionals Follow-up Study investigated the

relationship between plasma adiponectin levels and risk of myocardial infarction (MI).

- 3 Risk of MI was lowest in patients with the highest adiponectin levels (RR 0.39; P for trend <0.001).
- 4 The relationship was independent of family history of MI, BMI, diabetes, hypertension, HbA_{1c}, and C-reactive protein; adjustment for LDL and HDL cholesterol levels, however, attenuated the relationship.

5 The authors concluded that high plasma adiponectin levels are associated with lower risk of MI in men.

Pischon T, Girman CJ, Hotamisligil GS et al (2004) Plasma adiponectin levels and risk of myocardial function in men. *Journal of the American Medical Association* **291**(16): 1730–36

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Parental CVD can double risk of CVD in offspring

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

- 1 This prospective study examined the association of parental cardiovascular disease (CVD) with 8-year risk of offspring CVD disease.
- 2 All Framingham Offspring Study participants (aged ≥30 years) who were free of CVD, and both parents in

the original Framingham cohort, were enrolled in the study.

- 3 During follow-up of the 2302 participants, 164 men and 69 women had cardiovascular events.
- 4 Parental CVD independently predicted offspring cardiovascular events in middle-aged men and women.

5 Premature CVD (onset age <55 years in father, <65 years in mother) in at least one parent doubled (significantly) the risk of CVD for men and increased the risk for women by 70% (non-significant) over 8 years.

Lloyd-Jones DM, Nam BH, D'Agostino et al (2004) Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. *Journal of the American Medical Association* **291**(18): 2204–10

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Glucose metabolism and severity of CHD

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 This cross-sectional study looked at glucose metabolism in 234 men with normal glucose tolerance (NGT) and coronary heart disease (CHD) admitted to an academic medical centre in Italy for angiography.

2 Patients were divided into four groups based on coronary

angiography: no significant stenosis (42); 1-vessel disease (72); 2-vessel disease (64); 3-vessel disease (56).

3 Factors independently associated with the number of stenosed arteries were: levels of postload plasma glucose, HbA_{1c}, postload insulin, fasting insulin, and insulin resistance measured by homeostasis model assessment (P<0.001 for all).

4 Among patients with NGT and different extents of atherosclerotic disease, postload glycaemia and HbA_{1c} levels are significantly higher in those with more severe disease.

Sasso FC, Carbonara O, Nast R et al (2004) Glucose metabolism and coronary heart disease in patients with normal glucose tolerance. *Journal of the American Medical Association* **291**(15): 1857–62