EDITORIAL

The effect of intensive lipid lowering on coronary atheroma and clinical outcome

Emma S Houslay, Jaydeep Sarma, Neal G Uren

The association between raised plasma cholesterol and cardiovascular risk is well established, with consistent evidence associating LDL-cholesterol reduction with a reduction in primary and secondary cardiovascular events. It is believed that intensive lipid lowering may improve clinical outcomes further by acting to stabilise plaque and preventing plaque progression, ultimately reducing plaque vulnerability. However, it remains uncertain whether a continued clinical benefit occurs with intensive lipid lowering or if there is a threshold level below which no further benefit occurs.

Regardless of baseline cholesterol levels, therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) appears to reduce significantly the risk of death, myocardial infarction (MI) and stroke and the need for revascularisation in patients with coronary artery disease. The clinical benefits observed with up to a 35% reduction in LDL-cholesterol in large studies of high risk subjects such as WOSCOPS (40 mg pravastatin),¹ and in studies of those with established coronary disease such as 4S (20–40 mg simvastatin),² CARE,³ and LIPID (both 40 mg pravastatin),⁴ raised the issue of whether an even lower risk of coronary events might result from more intensive LDL-cholesterol reduction. The acute effect of intensive lipid lowering in unstable angina and non-ST elevation MI was studied in the MIRACL trial.⁵ Compared to placebo, 80 mg atorvastatin in patients with a baseline LDL-cholesterol of 3.0 mmol/l led to a 16% reduction in the composite end point of death/MI/refractory angina/re-hospitalisation over a 16-week period, suggesting that the benefit of statins may not be attributable to LDL lowering alone. More recently, the PROVE-IT trial data showed that 80 mg atorvastatin reduced clinical event rates in patients (n = 4162) with acute coronary syndromes when compared with 40 mg pravastatin, with a 16% relative risk reduction for all cause mortality, a trend which was evident just 30 days into the trial and consistent at 2 years of follow-up.⁶ A safety substudy of the trial confirmed that elevated liver enzymes, specifically alanine aminotransferase levels three times the upper level of normal or greater, were more common in the atorvastatin group (3.3% v 1.1%; p < 0.001), but no net excess in discontinuation due to increased creatine kinase levels or myalgia occurred.⁷

In stable coronary disease, the ALLIANCE trial randomised 2442 patients to either 80 mg

Heart 2007;93:149–151. doi: 10.1136/hrt.2006.105676

atorvastatin or to usual care over 4 years.⁸ In the intensive arm (lowering LDL-cholesterol to 2.5 mmol/l), a 14% relative reduction in the composite end point of all cardiac events (death/MI/resuscitated sudden death/revascularisation/hospitalisation with unstable angina) from 28% to 24% was seen, largely due to a relative reduction in non-fatal MI of 45%.⁸ The largest trial of intensive lipid lowering in stable coronary disease, the TNT trial, randomised 10 001 patients with documented coronary disease to either 10 or 80 mg atorvastatin over 5 years.⁹ The cohort receiving 80 mg atorvastatin achieved an LDL-cholesterol level of 2.0 mmol/l, compared to 2.6 mmol/l with 10 mg, with a 22% relative reduction in the primary end point (a composite of coronary heart disease death/non-fatal MI/resuscitated cardiac arrest) from 10.9% to 8.7% (p < 0.01). There was a reduction in non-fatal MI from 6.2% to 4.6% (p < 0.01) and a reduction in fatal and non-fatal stroke from 3.1% to 2.3% (p < 0.05), with a trend to a reduction in cardiovascular mortality from 2.5% to 2.0% (p = 0.09).⁹ Overall, all-cause mortality did not differ between the groups, although it is interesting to note that the coronary deaths were much lower than in other secondary prevention statin trials.

Most recently, in the IDEAL study (n = 8888), 80 mg atorvastatin did not result in a significant reduction in the (similar) primary end point of major coronary events when compared with 20 mg simvastatin in patients with a previous MI over a 6-year period.¹⁰ However, with the addition of stroke, revascularisation and hospitalisation with unstable angina to major cardiac events as a composite end point, a significant 16% reduction in all cardiovascular events was reported, consistent with the data from both PROVE-IT,⁶ and TNT.⁹ The safety of intensive lipid lowering is an issue these trials both highlight and put into perspective. The benefit of intensive lipid-lowering appears to be directly related to the extent of LDL-cholesterol lowering, but with the major additional effect seen in a reduction in non-fatal MI rather than a further reduction in mortality. With regard to the safety of an intensive lipid-lowering strategy in both TNT and IDEAL, there were more non-serious adverse events due to liver enzyme elevation in the 80-mg atorvastatin group resulting in drug discontinuation, but no excess of significant myopathy was seen.¹¹

Abbreviations: CRP, C-reactive protein; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IL-6, interleukin-6; M-CSF, macrophage-colony stimulating factor; MI, myocardial infarction; PPAR, peroxisome proliferator-activated receptor

See end of article for authors' affiliations

Correspondence to: Dr Neal Uren, Department of Cardiology, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK; nealuren@hotmail.com

Published Online First
11 October 2006

DOES INTENSIVE LIPID LOWERING MODIFY ATHEROSCLEROTIC PLAQUE?

Intensive lipid lowering with statins appears to modify atherosclerotic plaque load. In the ARBITER trial,¹² 161 patients were randomised to 40 mg pravastatin or 80 mg atorvastatin. At 12 months, the net change in carotid intima-media thickness with pravastatin and atorvastatin was +0.025 (0.017) versus -0.034 (0.021) mm ($p=0.03$), respectively, associated with greater LDL-cholesterol reduction and C-reactive protein (CRP) reduction in the atorvastatin arm.¹² Using magnetic resonance imaging of aortic and carotid plaques (comparing 20 mg and 80 mg simvastatin), Corti *et al* concluded from similar vessel wall areas at end point that the final LDL-cholesterol level determined the degree of plaque regression rather than statin dose itself, although the two comparator groups started from different LDL-cholesterol levels.¹³

The REVERSAL trial compared 40 mg pravastatin with 80 mg atorvastatin in 654 patients with coronary stenoses (>20% diameter), measuring single vessel atheroma volume by intravascular ultrasound at baseline and after 18 months of treatment.¹⁴ There was a significant difference in the median percentage change of atheroma volume, +2.7% with pravastatin versus -0.4% with atorvastatin ($p<0.05$) (25% v 46% reduction in LDL-cholesterol), respectively, confirming that intensive lipid lowering halted the progression of atheroma.¹⁴ Furthermore, the atheroma progression rate at any level of LDL-cholesterol was lower with atorvastatin than pravastatin, suggesting an additional anti-inflammatory effect with more intensive lipid lowering (a 36% reduction in CRP with atorvastatin, compared to 5% with pravastatin). Thus result was supported further by the progression of atheroma in the pravastatin arm, even in patients who achieved LDL-cholesterol levels below the US National Cholesterol Education Programme guideline level of 2.6 mmol/l. Recent data from the ASTEROID trial using 40 mg rosuvastatin has confirmed actual plaque regression with a 7% median reduction in per cent atheroma volume (with a 53% reduction in LDL-cholesterol) compared to baseline over 2 years.¹⁵ In this trial, it was interesting to note that a 15% increase in HDL-cholesterol also occurred.

THE PLEIOTROPIC EFFECTS OF STATINS

The lipid-lowering effect of statins is believed to retard vascular wall uptake of modified lipoproteins thus reducing atherosclerotic lesional lipid content and bulk. However, subgroup analysis of large clinical trials such as CARE suggests that statin-treated individuals have a lower cardiovascular risk than placebo-controlled subjects for the same cholesterol level.³ Pleiotropic effects unrelated to LDL-cholesterol lowering are attributed to statins such as modifying platelet and leukocyte integrin interactions, reducing thrombus formation, and promoting plaque stabilisation through a reduction in matrix metalloproteinase activity.¹⁶ Furthermore, a reduction in circulating inflammatory markers and in vascular smooth muscle cell hypertrophy and proliferation has been demonstrated with statin therapy along with improved endothelial function.¹⁷

While increased levels of macrophage-colony stimulating factor (M-CSF), interleukin-6 (IL-6) and CRP are well established in acute coronary syndromes,¹⁸ they also appear to be markers of plaque load in stable coronary disease. CRP produced by the liver through inflammatory cytokines such as IL-6 also reflects low-grade systemic inflammation. Elevated levels predict risk in stable and unstable coronary artery disease,^{19–20} and data from CARE and the AFCAPS/TexCAPS trials^{21–22} have shown that CRP levels are reduced in parallel with reduced cardiovascular risk with statin therapy. These

data suggest a decrease in systemic vascular inflammation with statins that is presumed to be dose-dependent.

CONCLUSIONS

The current evidence base confirms the benefit of statin therapy irrespective of baseline LDL-cholesterol levels with a strong case for intensive lipid lowering in all patients with coronary artery disease. Recent data pooled from 49 comparative studies of 10 mg versus 80 mg atorvastatin in 14 236 patients has confirmed the safety of such a strategy, quoting a myalgia rate of 1.4% and 1.5%, respectively, with no rhabdomyolysis.¹¹ Trials with other lipid-modulating drugs such as peroxisome proliferator-activated receptor (PPAR) agonists and cholesterol ester transfer protein inhibitors will question whether intensive LDL-lowering alone is sufficient, or whether a further improvement in outcomes may occur from interventions such as raising HDL-cholesterol. Given the non-statistical excess of non-cardiovascular deaths in the patients receiving 80 mg atorvastatin in TNT (but not in IDEAL), it may be that patients most likely to benefit from an intensive strategy should be identified independently from their baseline LDL-cholesterol level, rather than the current threshold approach. Given the data on the additional risk conferred from increased levels of inflammatory biomarkers, a decision to treat individual stable patients intensively could be made by measuring these markers of inflammation prior to starting treatment. In advance of a robust genetic risk-profiling methodology, this could be the best approach there is.

Authors' affiliations

E S Houslay, J Sarma, N G Uren, Department of Cardiology, Royal Infirmary of Edinburgh, Edinburgh, UK

Competing interests: None declared.

REFERENCES

- 1 Shepherd J, Cobbe SM, Ford I, *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;**333**:1301–7.
- 2 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;**344**:1383–9.
- 3 Lewis SJ, Sacks FM, Mitchell JS, *et al*. Effect of pravastatin on cardiovascular events in women after myocardial infarction: the cholesterol and recurrent events (CARE) trial. *J Am Coll Cardiol* 1998;**32**:140–6.
- 4 Lipid Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998;**339**:1349–57.
- 5 Schwartz GG, Olsson AG, Ezekowitz MD, *et al*. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**(13):1711–8.
- 6 Cannon CP, Braunwald E, McCabe CH, *et al*. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;**350**:1495–504.
- 7 Wiviott SD, Cannon CP, Morrow DA, *et al*, for the PROVE IT-TIMI 22 investigators. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy. *J Am Coll Cardiol* 2005;**46**:1411–16.
- 8 Koren MJ, Hunninghake DB. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the ALLIANCE study. *J Am Coll Cardiol* 2004;**44**:1772–9.
- 9 LaRosa JC, Grundy S, Waters DD, *et al*. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;**352**:1425–35.
- 10 Pedersen TR, Faegeman O, Kastelein JJ, *et al*. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study. *JAMA* 2005;**294**:2437–45.
- 11 Newman C, Tsai J, Szarek M, *et al*. Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients. *Am J Cardiol* 2006;**97**:61–7.
- 12 Taylor AJ, Sullenberger LE, Lee HJ, *et al*. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation* 2004;**110**:3512–17.
- 13 Corti R, Fuster V, Fayad ZA, *et al*. Effects of aggressive versus conventional lipid-lowering therapy by simvastatin on human atherosclerotic lesions. *J Am Coll Cardiol* 2005;**46**:106–12.

- 14 **Nissen SE**, Tuzcu EM, Schoenhagen P, *et al.* Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004;**291**:1071–80.
- 15 **Nissen SE**, Nicholls SJ, Sipahi I, *et al.* Effect of very high-intensity statin therapy on regression of coronary atherosclerosis (ASTEROID). *JAMA* 2005;**295**:1556–65.
- 16 **Takemoto M**, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arterioscler Thromb Vasc Biol* 2001;**21**:1712–19.
- 17 **Aikawa M**, Rabkin E, Sugiyama S, *et al.* An HMG-CoA reductase inhibitor, cerivastatin, suppresses growth of macrophages expressing matrix metalloproteinases and tissue factor in vivo and in vitro. *Circulation* 2001;**103**:276–83.
- 18 **Biasucci LM**, Vitelli A, Liuzzo G, *et al.* Elevated levels of interleukin-6 in unstable angina. *Circulation* 1996;**94**:874–7.
- 19 **Liuzzo G**, Biasucci LM, Gallimore JR, *et al.* The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med* 1994;**331**:417–24.
- 20 **Ridker PM**, Haughey P. Prospective studies of C-reactive protein as a risk factor for cardiovascular disease. *J Invest Med* 1998;**46**:391–5.
- 21 **Ridker PM**, Rifai N, Pfeffer MA, *et al.* Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1998;**98**:839–44.
- 22 **Downs JR**, Clearfield M, Weis S, *et al.* Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA* 1998;**279**:1615–22.

IMAGES IN CARDIOLOGY

doi: 10.1136/hrt.2006.094037

Left ventricular pressure–volume loops during mechanical alternans in a patient with dilated cardiomyopathy

A 34-year-old man was admitted to our hospital (Niigata University Medical and Dental Hospital, Niigata, Japan) with dyspnoea on exertion and pretibial oedema. The chest x ray showed cardiomegaly, pulmonary congestion and right pleural effusion. The echocardiogram showed enlargement and diffuse hypokinesis of the left ventricle. Cardiac enzyme levels were not raised on laboratory examination. Symptoms were alleviated with intravenous diuretics and catecholamines, then stabilised with oral diuretics, digoxin and enalapril.

Cardiac catheterisation was performed about 1 month after admission. Coronary arteries were normal, and an endomyocardial biopsy specimen did not show inflammation or any specific findings. The patient was diagnosed with idiopathic dilated cardiomyopathy. Left ventriculography was performed and the left ventricular pressure was simultaneously recorded using a micromanometer-tipped pigtail catheter. Apparent mechanical alternans was recorded in the pressure wave form (panel A) and visualised on left ventriculography. Left ventricular volume was calculated by the Kennedy's regression equation, and the pressure–volume loops of six consecutive beats (panel A, bidirectional arrow) were drawn. Panels B and C show the loops of three strong and three weak beats separately. The end-systolic pressure–volume points of strong beats were higher in pressure and smaller in volume than those of weak beats, suggesting that the strong and weak beats were associated with differences in contractility.

The alternating contractility during mechanical alternans was shown by drawing the left ventricular pressure–volume loops of the isolated canine heart. This is the first report of human left ventricular pressure–volume loops during mechanical alternans.

T Kashimura
M Kodama
Y Aizawa
kashi@med.niigata-u.ac.jp