ARBITER-2: judging the next step in lipid management

Statin therapy is established as the basis of lipid-lowering therapy in all patients with established atherosclerotic disease.[1] However, statin trials show that 50–70% of cardiovascular events cannot be prevented by statins alone.[2,3] This raises the question about the next step that should be taken to prevent further events in high-risk patients already on a statin.

The options that exist are to reduce levels of low-density lipoprotein cholesterol (LDL-C) further or to attempt to target other cardiovascular risk factors. The commonest approach to lipid management involves reducing LDL-C levels further (to 1.75 mmol/L from 2.5–3.0 mmol/L). Improvements in LDL-C levels deliver further reduction in events in chronic atherosclerosis. This can be seen by the 1.75 mmol/L *vs.* 1.0 mmol/L change seen in a comparison of the GREACE (Greek Atorvastatin and Coronary Events) and HPS (Heart Protection Study) studies respectively.[4] Even in the GREACE study, however, event reduction was only 50%.

Data from high to low dose statin comparator studies in acute atherosclerosis (acute coronary syndromes) are conflicting. A further reduction in events was seen in the PROVE-IT study with atorvastatin 80 mg (*vs.* pravastatin 40 mg)[5] but not in the Z phase of the A to Z study of simvastatin (80 mg *vs.* 40 mg based-protocols).[6] Thus, although the US guidelines (NCEP-ATP III; 2004) suggest lowering LDL-C further with statins in high-risk patients, this recommendation requires confirmation in further trials including patients with chronic as well as acute disease.[7] This is likely to come from the TNT (Treating to New Targets), IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) and SEARCH (Study of the Effectiveness of Additional Reduction in Cholesterol and Homocysteine with Simvastatin and Folic Acid/Vitamin B12) trials in the next two years.

Anthony S Wierzbicki

Other lipid-based approaches

The alternative method of reducing cholesterol through inhibition of cholesterol absorption with ezetimibe is likely to work based on epidemiological data and also those from trials such as POSCH (Program on Surgical Correction of Hyperlipidemia) with surgical ileal bypass, the LRC (Lipid Research Clinics) study with cholestyramine, and studies of enhanced carotid and coronary atheroma regression with combinations of statins and bile acid sequestrants. Formal proof of the efficacy of ezetimibe, however, will only come with the publication of the ENHANCE (carotid intima-media thickness in familial hypercholesterolaemia) and SEAS (Statin-Ezetimibe in Aortic Stenosis) studies.[8]

Raising HDL-C

Trials of additional therapies have failed, so far, to demonstrate convincingly that these approaches will succeed but there is another lipid-based approach which has strong epidemiological and trial-based validity. In epidemiological studies, levels of high-density lipoprotein cholesterol (HDL-C) up to 2.5 mmol/L have been found to be independently protective in reducing events. Lifestyle interventions that raise HDL-C levels also seem to be beneficial. Data on two HDL-C raising drugs show that: i) nicotinic acid in the Coronary Drug Project in a general population and ii) gemfibrozil in VA-HIT (the Veterans Affairs HDL Intervention Study) in a low HDL-C (0.87 mmol/L) and a low LDL-C (2.9 mmol/L) population, both reduced cardiovascular events by 20–25%, the latter with no effect attributable to action on LDL-C.[2] Fenofibrate in the Diabetes Atherosclerosis Intervention Study (DAIS) trial also reduced coronary atheroma progression on quantitative angiography. Data on combining HDL-C raising therapies with statin-based therapies, however, have been lacking. No fibrate-statin studies have so far been performed although one is underway (ACCORD) in patients

with diabetes. Recently, a study looking at nicotinic acid in patients already treated with statins was reported.

The ARBITER-2 (Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol) study recruited 167 patients with coronary heart disease. Few smoked (5%) but the trial population included many with the metabolic syndrome (55%), diabetes (20%) or hypertension (60%). All had been treated with simvastatin (35 mg average) to reduce LDL-C (2.25 mmol/L) below European (2.5 mmol/L) and British (3.0 mmol/L) targets.[9] The patient group recruited mimicked many features of that found in the lowest quartile of the HPS study. The patients had mild hypertriglyceridaemia (1.85 mmol/L) but acceptable HDL-C levels (1.0 mmol/L). After one year of treatment with a moderate dose (1 g/day) of prolonged release nicotinic acid, which raised HDL-C by 21%, progression of atherosclerosis – as defined by carotid intima-media thickness (IMT) – was significantly reduced and statistically stopped in the group receiving nicotinic acid.

As both carotid IMT and, indeed, many quantitative coronary angiography trials have consistently predicted later benefit in outcome studies for all lipid-lowering drugs, including resins, fibrates and statins, these two measures are considered good surrogate markers for disease. The effects seen in ARBITER-2 were significant, occurred quickly and were observed in a small study. The effects are comparable and may be superior to those observed in many previous carotid IMT studies. Thus, this study gives justification for raising further the target HDL-C levels recommended in international guidelines for patients with coronary heart disease and additional metabolic risk factors. The formal proof of the benefit of raising HDL-C with nicotinic acid in addition to a statin will have to wait until an end point study has been carried out. Meanwhile, the ARBITER-2 results are very encouraging pilot data for the validity of such an approach to cardiovascular prevention.

Conflict of interest

Dr Wierzbicki has received lecture honoraria, travel and research grant support from Astra-Zeneca, Bristol-Myers-Squibb, Glaxo-Smith-Kline, Fournier, Merck GmBH, Mitsubishi, Merck-Sharp & Dohme, Pfizer, Novartis, Sanofi-Aventis, Schering-Plough, Solvay, Roche and Takeda.

References

1. Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. *Heart* 1998;**80**(suppl 2):S1-S29.
2. Wierzbicki AS. Raising high-density lipoprotein. *Int J Clin Pract* 2004 **58**:817-19.
3. Wierzbicki AS, Mikhailidis DP. Beyond LDL-C – the importance of raising HDL-C. *Curr Med Res Opin* 2002;**18**(1):36-44.
4. Athyros VG, Papageorgiou AA, Mercouris BR *et al*. Treatment with atorvastatin to the National Cholesterol Educational Program goals versus usual care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) Study. *Curr Med Res Opin* 2002;**18**:220-8.
5. 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.
6. de Lemos JA, Blazing MA, Wiviott SD *et al*. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;**292**:1307-16.
7. Grundy SM, Cleeman JI, Merz CN *et al*. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;**110**:227-39.
8. Wierzbicki AS. Ezetimibe: a new addition to lipid-lowering therapy. *Int J Clin Pract* 2003;**57**:653-5.
9. 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.

Anthony S Wierzbicki
Senior Lecturer in Chemical Pathology
St Thomas' Hospital, Lambeth Palace Road,
London, SE1 7EH.
(email: Anthony.Wierzbicki@kcl.ac.uk)

Br J Cardiol 2005;**12**:9–10