The large clinical trials of LDL-cholesterol lowering conducted over the past decade have demonstrated that therapy with various statins (3-hydroxy-3-methylglutaryl coenzyme A reductase [HMG CoA] reductase inhibitors) is a highly effective and well tolerated treatment for reducing cardiovascular morbidity and mortality. These studies have consistently shown that there is a direct relationship between the magnitude of the reduction in LDL-cholesterol levels and the reduction in CHD risk and furthermore, the clinical benefits of statin therapy are largely independent of the baseline levels of LDL-cholesterol. Thus, significant reductions in the relative risk of cardiovascular events have been observed among patients whose baseline concentrations of total and LDL-cholesterol were close to or within the so-called normal range. Based on these results there has been a revision of treatment guidelines to reduce CHD risk in patients with dyslipidaemia or other risk factors for cardiovascular disease. The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) recommended modifications to the earlier treatment algorithm so that for very high risk persons, an LDL-cholesterol goal of <1.8 mmol/L (70 mg/dL) is a therapeutic option, and this therapeutic option extends also to patients at very high risk who have a baseline LDL-cholesterol <2.6 mmol/L (100 mg/dL). For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-cholesterol goal is <3.4 mmol/L (130 mg/dL), but an LDL-cholesterol goal <2.6 mmol/L (100 mg/dL) is now a therapeutic option on the basis of recent trial evidence. In the European Joint Task Force guidelines, target LDL-cholesterol levels in patients with clinically established cardiovascular disease and/or diabetes mellitus were reduced from <3.0 mmol/L (115 mg/dL), recommended in their 1998 publication to <2.5 mmol/L (100 mg/dL) in their current guidelines.

Even before these more aggressive lipid treatment guidelines, surveys in the USA showed that many high risk patients did not achieve LDL-cholesterol target levels. Similar results were found in the European Action on Secondary Prevention by Intervention to Reduce Events (EUROASPIRE II) study, which showed that approximately 50% of high-risk patients in Europe were not achieving the goal for LDL-cholesterol set in the previous European Guidelines in 2001. Some of the explanations for the shortfall in LDL-cholesterol goal attainment include selection of lipid-modifying therapy with inadequate efficacy, poor patient compliance, and reluctance to titrate to higher doses. In light of the clear evidence that CHD risk reduction is contingent upon effective reduction on LDL-cholesterol there is a need to educate both physicians and patients in this respect.

**Statins and efficacy in LDL reduction**

Considering that the starting dose of statin should be sufficiently effective to achieve the lipid goal in the majority of patients, rosuvastatin is the most effective of all the statins in reducing LDL-cholesterol across the dose range as shown in the STELLAR study. Furthermore, the Measuring Effective Reduction in Cholesterol Using Rosuvastatin therapy (MERCURY I) study found that significantly more patients treated with rosuvastatin 10 mg/day achieved the European goal (2003) for LDL-cholesterol compared with those receiving atorvastatin 10 mg/day, and this difference was particularly marked among those patients considered to be at greatest risk for coronary heart disease. In a meta-analysis of pooled data from 6743 patients included in five studies from the Direct Statin Comparison of LDL-C Values: an Evaluation of Rosuvastatin therapy (DISCOVERY) programme, rosuvastatin 10 mg was confirmed to be significantly (p<0.001) more effective than atorvastatin 10 mg in achieving 2003 European goals for both LDL-cholesterol and total cholesterol. Rosuvastatin had a safety profile comparable with those of other statins in these and other studies.

**Rosuvastatin in Asian patients**

There has been some concern that the plasma concentrations and systemic exposure to rosuvastatin were found to be approximately 2-fold higher in Japanese subjects living in Japan compared with white subjects in Western Europe or the United States. Similar findings were reported in Chinese, Malay, and Asian-Indian subjects living in Singapore compared with white subjects. The reason for this difference in
pharmacokinetics has not been fully established and did not appear to be related to polymorphisms in one of the drug transporter proteins studied but may be related to another one known as breast cancer resistance protein (BCRP). It should be noted that the variations in plasma levels and systemic exposure to rosuvastatin are greater between individuals within any ethnic group than between ethnic groups so the advice to restrict the dose to a maximum of 20 mg daily in Asian patients is not entirely rational.

Despite these differences in pharmacokinetics between Asians and western subjects there does not appear to be any difference in efficacy or safety with rosuvastatin. Studies in Japanese patients with hypercholesterolaemia have shown a similar dose-response relationship to that in western patients, with reductions in LDL-cholesterol levels of 49.7% to 66.0% with rosuvastatin 10-40 mg Similar results were reported with rosuvastatin 10-40 mg in an open-label study of 37 Japanese patients with heterozygous familial hypercholesterolaemia, with significant (p<0.001) reductions from baseline in LDL-cholesterol of 49.2% to 56.7%. The safety of rosuvastatin is well established with a similar safety profile to that of comparator statins in data from 12,400 patients included in the multinational rosuvastatin phase II/III programme and a retrospective observational study using an administrative managed care claims database covering 9 million members in the USA.

Clinical implications

The benefits of aggressive lipid lowering with high doses of atorvastatin were established in the Treating to New Targets (TNT) study in patients with stable coronary heart disease, the clinical endpoint study in the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110: 227-39


6. Foleky KA, Simpson RJ, Jr, Crouse JR, 3rd, Weiss TW, Markson LE, Alexander CM. Effectiveness of statin titration on low-density lipoprotein cholesterol goal attainment in patients at high risk of atherogenic events. Am J Cardiol 2003; 92: 79-81


