Despite a huge number of studies that have established the beneficial effects of statins in cardiovascular diseases, the mechanism of action of these drugs remains puzzling and indeed one of the most challenging research topics for clinicians and biologists in cardiology.

Statins are highly effective in lowering concentrations of serum cholesterol through 3-hydroxymethylglutaryl coenzyme A reductase inhibition. But statins also exert numerous lipid-independent effects. These ‘pleiotropic’ actions include improved endothelial function, stabilization of vulnerable plaques, and anti-inflammatory and antithrombotic effects [1]. Myocardial effects have also been reported including modulation of signalling pathways involved in hypertrophic remodelling of the heart [2], together with cardioprotective effects, notably against oxidative stress [3]. These drugs also show antiarrhythmic effects that may result from a reduction of the arrhythmogenic substrate, notably fibrosis in the context of atrial fibrillation [4,5]. Cholesterol is an important determinant in the function of ionic channels and in the electrical properties of membranes. Recent studies report that alterations in membrane-cholesterol content are associated with marked changes in potassium channel activity both in endothelial vascular cells [6] and cardiac myocytes [7]. These effects of statins on ion channels could lead to vasodilatation or modulation of myocardial repolarization and antiarrhythmic properties.
During an acute coronary syndrome (ACS) plasma cholesterol levels decrease, and may be explained by a parallel increase in low-density-lipoprotein (LDL) receptor activity and increased cholesterol catabolism. This could result in an enhanced delivery of cholesterol to cells involved in tissue-repair mechanisms, or may reflect non-specific acute phase responses, for instance secondary to the inflammatory phenomenon [8—10].

Rosuvastatin is a recent statin with a potent cholesterol-lowering effect and [good?] safety profile, as shown in different trials upon switching from alternative statins that were not fully effective. Rosuvastatin is a synthetic hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor with distinctive pharmacological (relatively hydrophilic) and pharmacokinetic properties. In comparison with other statins, rosuvastatin exhibits a greater number of binding interactions with HMG-CoA reductase, a high affinity for the enzyme's active site, and potent inhibition of cholesterol synthesis in hepatocytes [11]. In a broad spectrum of adult patients with dyslipidaemias, several clinical studies have shown that rosuvastatin (5—80 mg) effectively reduced concentrations of total cholesterol, triglycerides, LDL-cholesterol (LDL-C), non—high-density lipoprotein cholesterol (non—HDL-C), and increased apolipoprotein (apo) A-I and HDL-C [12,13]. Compared with other statins, rosuvastatin is the most potent, significantly increasing apo A-I by nearly 9% [13]. In addition to effectively reducing plasma cholesterol and LDL levels, a considerable clinical interest has been developed with rosuvastatin for its ability to increase concentrations of HDL-C and apo A-I. It is well established that HDL bears an inverse relationship to the development of atherosclerotic coronary heart disease [14]. Apo A-I is a major protein of HDL, and the cardioprotective effects of HDL have been attributed largely to the ability of apo A-I—containing HDL particles to initiate cholesterol efflux and thereby facilitate the removal of excess cholesterol from peripheral tissues and its delivery to the liver for elimination through the reverse cholesterol transport pathway. The other potent statin, atorvastatin, has little or no ability to increase concentrations of HDL-C, and this may be a disadvantage in patients with metabolic syndrome or diabetes, in whom low HDL-cholesterol is a key feature.

Recently, the ECLIPSE (Evaluation to Compare Lipid lowering effects of rosuvastatin and atorvastatin In force titrated subjects: a Prospective Study of Efficacy and tolerability) study showed that rosuvastatin (10—40 mg) achieved more frequently the NCEP ATP III LDL-C goal of <100 mg/dL (2.5 mmol/L) compared to atorvastatin (10—80 mg), with the same tolerability in high-risk patients with hypercholesterolaemia [15]. This is in line with data from the DISCOVERY (Direct Statin Comparison of LDL-C Values: An Evaluation of Rosuvastatin Therapy Compared with Atorvastatin) trial [16], which showed that rosuvastatin 10 mg was more potent in decreasing LDL-C and total cholesterol and in increasing HDL-C than atorvastatin 10 mg in a 12-week randomized trial including more than 900 subjects with hypercholesterolaemia who were at high risk for coronary heart disease.

Apart from its potent efficacy on lipid parameters, rosuvastatin exerts a variety of so-called ‘pleiotropic’ actions that may result in clinical benefit. A substantial number of experimental and clinical studies have indicated favourable effects of rosuvastatin on endothelial function, oxidized LDL, inflammation, plaque stability, vascular remodelling, haemostasis, and the myocardium [17]. Whether the established ‘pleiotropy’ and/or lipid-lowering efficacy of rosuvastatin may translate into reduced morbidity and mortality remains to be demonstrated in ongoing clinical trials. At present, no large-scale primary or secondary prevention clinical trials document either its long-term safety or effectiveness in preventing cardiovascular events.

The design of the CENTAURUS study [18] presented in this issue of Archives of Cardiovascular Diseases will provide further data on the relative efficacy of rosuvastatin and atorvastatin on the apolipoprotein B:A ratio (apoB/apoA-1) in patients with an ACS. Yusuf et al. [19] clearly demonstrated in the worldwide INTERHEART study that the apoB/apoA-1 ratio was the strongest predictor of myocardial infarction, and that this ratio was a better predictor than other relevant factors such as smoking, hypertension or diabetes. While the predictive value of this ratio has been poorly evaluated in patients post-ACS it is a predictor of vascular events in primary prevention [20]. In the LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease) trial [21], apoB and the combination of total and HDL-C were the most important lipid parameters associated with event reduction in secondary prevention. The CORALL (COMpare the effect of Rosuvastatin with Atorvastatin on apoB/apoA-1 ratio in patients with Type 2 diabetes mellitus and dyslipidaemia) study [22] showed that rosuvastatin (10—40 mg) led to a greater reduction of apoB/apoA-1 compared with atorvastatin (10—80 mg; −40.5% vs −35.8%, p < 0.05 at week 18) in patients with type 2 diabetes and dyslipidaemia but without an ACS. Recently, rosuvastatin combined with candesartan reduced plaque area in a diabetes-accelerated atherosclerosis mouse model [23].

As stated [18], the concentration of high-sensitivity C-reactive protein (hs-CRP) after an ACS seems to be an independent predictor of cardiovascular events beyond the LDL-C level. The comparative effect of rosuvastatin and atorvastatin on this inflammatory marker (secondary outcome) will be evaluated in this trial, including more than 1000 patients with an ACS who were followed for 3 months. However, the CENTAURUS study was not designed to solve the question as to whether the decrease of hs-CRP protects from cardiovascular events after an ACS independently of any LDL-C reduction because of a lack of power and a too short follow-up. The JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) study [24] is a randomized, double-blind, placebo-controlled primary prevention trial of rosuvastatin (20 mg) among persons with average to low levels of LDL-C who were at increased cardiovascular risk due to elevated plasma concentrations of the inflammatory biomarker hs-CRP. The results from this study will provide important and clinically relevant information on primary prevention among patients (>17 000) who do not currently qualify for lipid-lowering therapy. However, this study has been interrupted prematurely (evidence of benefit?). Finally, the importance and need for early initiation of statin therapy after an ACS has been demonstrated in a meta-analysis [25]. These data support intensive LDL-C
reduction post-ACS. If the CENTAURUS trial is able to provide information on the ability of rosuvastatin to decrease the apoB/apoA-1 ratio in ACS patients over atorvastatin, this will lengthen the window of opportunity to address this ratio before hospital discharge but its prognostic value will still be unavailable.

References


