Efficacy and safety of rosuvastatin in the management of dyslipidemia

Paolo Rubba
Gennaro Marotta
Marco Gentile

Department of Clinical and Experimental Medicine, Federico II University of Naples, Italy

Abstract: Rosuvastatin is a synthetic statin that represents an advance in the pharmacologic and clinical properties of statins. Relative to other statins, rosuvastatin possesses a greater number of binding interactions with HMG-CoA reductase and has a high affinity for the active site of the enzyme. As with other statins, serious adverse effects with rosuvastatin therapy are uncommon and primarily involve effects on the liver and skeletal muscle. The risk increases with increasing dosages and coadministration with other drugs interacting with the same metabolic pathway. The degree of LDL reduction is important to achieve the treatment goals suggested by international guidelines. Among the most potent statins, rosuvastatin is capable of getting the majority of patients to their LDL cholesterol goals. In addition, rosuvastatin has been found effective in reducing small-dense LDL, C-reactive protein and in increasing HDL cholesterol levels. Controlled clinical trials using vascular end-points have been performed. In particular, a study demonstrated that rosuvastatin therapy could slow progression and/or cause regression of carotid intima-media thickness over 2 years in middle-aged individuals with a low Framingham risk score (FRS) and mild to moderate subclinical atherosclerosis. A primary prevention study (JUPITER) was stopped before the programmed end of the study, because of excess benefit for high-risk individuals receiving rosuvastatin treatment. It is suggested that pronounced LDL reduction, in association with significant HDL cholesterol increase, are the bases of a marked preventive action of rosuvastatin. The results from JUPITER support the use of rosuvastatin for primary cardiovascular prevention, in overweight men and women, with near to normal LDL cholesterol and high CRP. There is now evidence of benefit from rosuvastatin treatment for a wide segment of the general population at intermediate cardiovascular risk. In absolute numbers, this segment represents the main source of cardiovascular events: on the basis of JUPITER results, it is expected that treatment target and potential candidates to statin therapy will be revaluated and redefined.

Keywords: cardiovascular prevention, cholesterol, high-density lipoprotein, C-reactive protein, vascular end-point, overweight

Rosuvastatin: a new drug

During the last 20 years evidence has accumulated showing dramatic reduction in cardiovascular risk using 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins") to lower levels of low-density lipoprotein (LDL) cholesterol. In general, a 21% reduction in the risk of major cardiovascular events is associated with every 1 mmol/L (39 mg/dL) decrease in LDL cholesterol.[1] However, despite this therapeutic success, the residual risk of major cardiovascular events remains high. This is the basis of scientific and public health interest in new drugs and intervention strategies aimed at reducing the still high cardiovascular risk in the population.

Rosuvastatin is a synthetic statin that represents an advance in the pharmacologic and clinical properties of statins. Relative to other statins, rosuvastatin possesses a greater number of binding interactions with HMG-CoA reductase and has a high affinity for the active site of the enzyme. Rosuvastatin is relatively hydrophilic and is selectively

Correspondence: Paolo Rubba
Department of Clinical and Experimental Medicine, University "Federico II" Medical School, Nuovo Policlinico – Edificio 1, Via Pansini, 5 – 80131 Naples, Italy
Tel +39-081-7462300
Fax +39-081-7462300
Email rubba@unina.it

taken up by, and active in, hepatic cells. Rosuvastatin has the longest terminal half-life among statins and is only minimally metabolized by the cytochrome P450 (CYP 450) enzyme system, with no significant involvement of the 3A4 enzyme. Consistent with this finding is the absence of clinically significant drug interactions between rosuvastatin and other drugs known to inhibit CYP 450 enzymes.[2,3]

Safety, tolerability

The benefits of statins are well documented. However, lipid-lowering drugs may cause myopathy, even rhabdomyolysis, the risk of which is increased by certain interactions. Rosuvastatin is excreted mainly unchanged, and its plasma concentrations are not significantly increased by cytochrome inhibitors.

Other clinically relevant intractions are nevertheless possible. Cyclosporine (INN, ciclosporin) inhibits CYP3A4, P-glycoprotein (multidrug resistance protein 1), organic anion transporting polypeptide 1B1 (OATP1B1), and some other hepatic uptake transporters. Gemfibrozil and its glucuronide also inhibit OATP1B1. A genome-wide search demonstrated a strong association between myopathy with a single nucleotide polymorphism located within SLCO1B1, which encodes OATP1B1.[4] One common variant in SLCO1B1 is associated with increased risk of statin-induced myopathy. The effects of cyclosporine and gemfibrozil, leading to inhibition of statin biliary excretion, explain the increased plasma statin concentrations and, together with pharmacodynamic factors, the increased risk of myotoxicity when coadministered with statins. In addition, inhibitors of hepatic uptake transporters may decrease the benefit/risk ratio of statins by interfering with their entry into hepatocytes, their site of action.[5–7]

In particular, rosuvastatin exposure was significantly increased in transplant recipients on antirejection regimen including cyclosporine. Cyclosporine inhibition of OATP-C-mediated rosuvastatin hepatic uptake may be the mechanism of this drug-drug interaction. Coadministration of rosuvastatin with cyclosporine needs to be undertaken with caution.[8]

A potential interaction between rosuvastatin and amiodarone, leading to elevated serum transaminase levels, has been suggested.[9]

The safety and tolerability of rosuvastatin were assessed using data from 12,400 patients who had received 5 to 40 mg of rosuvastatin in a multinational phase II/III program, which represented 12,212 patient-years of continuous exposure to rosuvastatin. An integrated database was used to examine adverse events and laboratory data. In controlled clinical trials with comparator statins, 5 to 40 mg of rosuvastatin showed an adverse event profile similar to those for 10 to 80 mg of atorvastatin, 10 to 80 mg of simvastatin, and 10 to 40 mg of pravastatin.

Clinically significant elevations in alanine aminotransferase (>3 times the upper limit of normal) and creatine kinase (CK) (>10 times the upper limit of normal) were uncommon (≤0.2%) in the groups that received rosuvastatin and comparator statins. Myopathy (CK >10 times the upper limit of normal with muscle symptoms) possibly related to treatment occurred in approximately 0.03% of patients who took rosuvastatin at doses up to 40 mg. Incidence of proteinuria during rosuvastatin treatment was comparable to that seen with other statins, and the development of proteinuria was not predictive of acute or progressive renal disease. No deaths in the program were attributed to rosuvastatin, nor did rhabdomyolysis occur in patients who received 5 to 40 mg of rosuvastatin.[10]

Myalgia, in the absence of CK elevation, is among the reasons leading patients to discontinue statins. Data from systematic reviews, meta-analyses, clinical and observational trials, and post-marketing surveillance indicate that statin-associated myalgia affects approximately 5.0% of patients, as myopathy in 0.1% and as rhabdomyolysis in 0.01%. In the case of myalgia it is recommended that patients undergo: (1) creatine kinase measurements and monitoring; (2) statin dosage reduction, discontinuation, and rechallenge; and (3) alternate-day therapy.[11]

A retrospective study evaluated tendon manifestations in statin-treated patients. Data from 31 French Pharmacovigilance Centers from 1990 to 2005 included adverse effects involving patient's tendons. Data were collected from 96 patients with tendon manifestations (median age of 56 years), namely tendonitis (n = 63) and tendon rupture (n = 33). Tendonopathy more often occurred within the first year after statin initiation (59%). Tendon manifestations were related to rosuvastatin in five cases. Statin was reinitiated in 7 patients receiving different statin treatment, resulting in recurrence of tendonopathy in all cases. This patient series suggests that statin-attributed tendonous complications are relatively rare, considering the huge number of statin prescriptions. Prescribers should be aware of these complications related, particularly in risky situations, including physical exertion and association with medications known to increase the toxicity of statins.[12]

As with other statins, serious adverse effects with rosuvastatin therapy are uncommon and primarily involve effects on the liver and skeletal muscle. The risk increases with increasing dosages and coadministration with other drugs

interacting with the same metabolic pathway. In the case of less than adequate reduction in LDL cholesterol levels with statin therapy of moderate potency, the clinician can up-titrate the dose of the initial statin, switch to a combination therapy (for example, including ezetimibe) and carefully monitor for adverse effects, or start a lower dose of a more potent statin (rosuvastatin or atorvastatin). The decision is based on the degree of lipid lowering required and on safety, cost, and compliance considerations.[13]

Dose, titration, target

The degree of LDL reduction is important to achieve the treatment goals suggested by guidelines. The NCEP III recommends a goal of less than 100 mg dL for patients at high risk for coronary heart disease. In Europe, the Joint European Societies' indicate a LDL cholesterol goal of less than 116 mg/dL. On the basis of available clinical trials, there is no evidence that achieving and maintaining such low levels of LDL cholesterol result in excess adverse effects. Among the most potent statins, rosuvastatin is capable of getting the majority of patients to their LDL cholesterol goals.[14]

Patients at very high risk for coronary artery disease benefit from treatment that lowers LDL cholesterol plasma levels below 1.81 mmol/L (70 mg/dL) and the NCEP III recommendations were amended to incorporate this. To reach these more aggressive goals and plasma LDL cholesterol reductions, more aggressive therapies will be required. To implement more aggressive treatment there is indication to start with one of the more potent statins, especially rosuvastatin or atorvastatin. These more potent statins appear to be safe, even when used at higher doses. The incidence of myopathy and rhabdomyolysis, as documented in long-term clinical trials, is $<0.1\%$ and $<0.01\%$, respectively.[15]

Rosuvastatin was introduced in the market more recently than other statins and most clinical trials used atorvastatin as the best available reference treatment. A double-blind, multicenter, randomized trial compared rosuvastatin and atorvastatin for reducing LDL cholesterol in adults with hypercholesterolemia and a high risk of coronary heart disease. At 24 weeks, LDL cholesterol was reduced significantly more with 80 mg rosuvastatin than with atorvastatin 80 mg (60% vs 52%). At 12 weeks, rosuvastatin 10 mg reduced LDL cholesterol significantly more than atorvastatin 10 mg (47% vs 35%). Therefore, more patients receiving rosuvastatin achieved LDL cholesterol goals and the effects of the two agents on triglycerides were similar.[16] A parallel decrease of the serum levels of non-high density lipoprotein (HDL) cholesterol and apolipoprotein-B has also been demonstrated.[17]After 6 week treatment of rosuvastatin at different dosages, non-HDL cholesterol was reduced in the range of 42% to 51% and apolipoprotein-B in the range of 37% to 45%. A treatment target of 90 mg/dL has been proposed for apolipoprotein-B.[18]

A multinational trial on hypercholesterolemic patients (n = 3140) with coronary heart disease, atherosclerosis, or type 2 diabetes assessed the effects of switching to low doses of rosuvastatin from commonly used doses of atorvastatin, simvastatin, and pravastatin on LDL cholesterol goal achievement in high-risk patients. The primary efficacy measure was the proportion of patients reaching the Joint European Societies' LDL cholesterol goal (<116 mg/dL) at week 16. Significant improvement in LDL cholesterol goal achievement was found for patients who switched to rosuvastatin 10 mg, compared with those who remained on atorvastatin 10 mg (86% vs 80%), simvastatin 20 mg (86% vs 72%), and pravastatin 40 mg (88% vs 66%), and between patients switched to rosuvastatin 20 mg and those who remained on atorvastatin 20 mg (90% vs 84%). Similar results were found for achievement of the European combined LDL cholesterol and total cholesterol goals and NCEP III LDL cholesterol goals.[19]

Rosuvastatin was tested in patients with severe hypercholesterolemia who are relatively refractory to lipid-lowering treatment. Heterozygous familial hypercholesterolemia (HFH) is a genetic disorder, associated with severe hypercholesterolemia and increased risk of early coronary artery disease. A study compared atorvastatin and rosuvastatin in reducing LDL cholesterol in HFH: 623 patients were randomized to 20 mg/day of atorvastatin (n = 187) or rosuvastatin (n = 436) with forced titration at 6-week intervals to 80 mg/day. At week 18, rosuvastatin therapy produced a greater reduction in LDL cholesterol (-57.9% vs -50.4%; $p < 0.001$) and a greater increase in HDL cholesterol (12.4% vs 2.9%) than atorvastatin. Rosuvastatin also produced significantly greater reductions in apolipoprotein-B, as well as a significantly greater increase in apolipoprotein A-I. More patients with HFH and coronary artery disease achieved the NCEP III goal of LDL cholesterol <100 mg/dL (<2.6 mmol/L) on rosuvastatin 40 and 80 mg than atorvastatin 80 mg (17%, 24%, and 4.5%, respectively). High-sensitivity C-reactive protein (CRP) median values were reduced by 33% to 34% in both the 80-mg rosuvastatin- and atorvastatin-treated groups.[20]

Another multicenter study assessed efficacy and safety of a fixed dose of rosuvastatin (40 mg) in 1380 patients with severe hypercholesterolemia, including HFH. Adult patients

with fasting LDL cholesterol between 190 and 260 mg/dL and triglycerides below 400 mg/dL received rosuvastatin 40 mg for 48 to 96 weeks. At 12 weeks, 83% of patients achieved NCEP ATP III LDL cholesterol goals, which were maintained during 2 to 4 years. At 4 years, LDL cholesterol was reduced by 54% and HDL cholesterol increased by 13%.[21]

As shown previously, rosuvastatin produces favorable effects on HDL cholesterol, which is an independent marker of cardiovascular risk. This has been evaluated in patients with the metabolic syndrome (MS), a constellation of coronary risk factors, including low HDL cholesterol. A post hoc analysis of data from a 6-week, randomized, open-label, parallel-group, comparative trial (Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin [STELLAR]) assessed the effects of rosuvastatin and atorvastatin on plasma lipids in hypercholesterolemic patients (LDL cholesterol between 160 and 250 mg/dl; triglycerides below 400 mg/dL) who had at least 3 of the 5 of the NCEP III criteria for MS. Of 2268 patients, 811 met criteria for MS. Percent reductions in LDL cholesterol were of 55% in the rosuvastatin 40-mg group. In patients with MS, triglyceride reductions ranged from 22% to 34% with rosuvastatin, and from 23% to 33% with atorvastatin. HDL cholesterol increased by 8% to 11% with rosuvastatin, and 5% to 9% with atorvastatin.[22]

The mechanism by which rosuvastatin increases HDL cholesterol is unclear. To clarify this, 12 men with the metabolic syndrome were studied in a randomized, double-blind, crossover trial of 5-week therapeutic periods with placebo, 10 mg/day rosuvastatin, or 40 mg/day rosuvastatin, with 2-week placebo washout between each period. Compared with placebo, there was a significant dose-dependent increase in HDL cholesterol, HDL particle size, and concentration of HDL particles containing apolipoprotein-I. The increase in apolipoprotein-I concentration was associated with significant dose-dependent reductions in triglyceride concentration and apolipoprotein-I fractional catabolic rate, with no changes in apolipoprotein-I production rate. There was a significant dose-dependent reduction in the fractional catabolic rate of HDL particles containing both apolipoprotein A-I and A-II, with a concomitant reduction in apolipoprotein-I: apolipoprotein-II production rate, and hence no change in apolipoprotein-I:apolipoprotein-II concentration. Thus, Rosuvastatin dose-dependently increased plasma HDL cholesterol and apolipoprotein-I concentrations in the metabolic syndrome. This could relate to the reduction in plasma triglycerides with remodeling of HDL particles and reduction in apolipoprotein-I fractional catabolism.[23]

Another study compared the effects of daily doses of rosuvastatin 40 mg with atorvastatin 80 mg during a 6-week period on HDL subpopulations in 306 hyperlipidemic men and women. Other studies had previously shown that increased levels of large alpha-1 and alpha-2 HDLs decrease the risk of coronary heart disease and protect against progression of coronary atherosclerosis. In this study, both statins caused significant increases in large alpha-1 and decreases in small pre-beta-1 HDL levels; however, increases in the 2 large HDL particles were higher for rosuvastatin than atorvastatin (alpha-1, 24% vs 12%; alpha-2, 13% vs 4%). Statin-induced increases in alpha-1 and alpha-2 correlated with increases in HDL cholesterol, whereas decreases in pre-beta-1 were associated with decreases in triglycerides. In subjects with low HDL cholesterol ($<$40 mg/dL for men, $<$50 mg/dL for women, n = 99), increases in alpha-1 were 32% vs 11%, and in alpha-2, 21% vs 5% for rosuvastatin and atorvastatin, respectively. Therefore, both statins, given at their maximal doses, favorably alter the HDL subpopulation profile, with rosuvastatin being more effective than atorvastatin.[24]

The effects of rosuvastatin on triglyceride rich lipoproteins and HDL were evaluated in patients with combined dyslipidemia and insulin resistance, before and after 3 months' treatment with gemfibrozil (1200 mg/day) or rosuvastatin (40 mg/day) with regard to: (1) steady-state plasma glucose concentration at the end of a 180-minute infusion of octreotide, insulin, and glucose; (2) fasting lipid, lipoprotein, and apolipoprotein concentrations; and (3) day-long glucose, insulin, triglyceride, and remnant lipoprotein cholesterol concentrations in response to breakfast and lunch. The two groups were similar at baseline in terms of age, gender, body mass index and measurements of carbohydrate and lipoprotein metabolism. Neither gemfibrozil nor rosuvastatin enhanced insulin sensitivity or lowered day-long glucose and insulin concentrations in insulin-resistant patients with combined dyslipidemia, but both drugs significantly decreased fasting triglyceride concentrations. Only rosuvastatin treatment significantly reduced fasting LDL cholesterol, apolipoprotein B-100, apolipoprotein C-III, apolipoprotein C-III:B particles, the apolipoprotein B-100:apolipoprotein A-I ratio, and increased apolipoprotein A-I. The degree of improvement in fasting and postprandial remnant lipoprotein cholesterol concentrations was relatively greater ($p < 0.05$) in rosuvastatin-treated patients.[25]

Small dense LDL (sdLDL) is a highly atherogenic sub-fraction of LDL, which is often increased in hypertriglyceridemic patients. In a post hoc sub-analysis of an open-label study, the effect of daily oral doses of rosuvastatin

40 mg and atorvastatin 80 mg on sdLDL cholesterol were compared, over a 6-week period in 271 hyperlipidemic patients. Rosuvastatin was ($p < 0.01$) more effective than atorvastatin in decreasing sdLDL cholesterol (−53% vs −46%), the two statins caused similar decreases in triglyceride levels (−24% and −26%).[26]

In general, statins decrease CRP in addition to LDL cholesterol, which may further decrease coronary heart disease risk. Rosuvastatin was compared with atorvastatin in achieving a combined target of LDL cholesterol <70 mg/dL and CRP <2 mg/L in 509 patients with type 2 diabetes mellitus. CRP decreased vs baseline in both treatment groups. More patients treated with rosuvastatin achieved the combined end point of LDL cholesterol <70 mg/dL and CRP <2 mg/L compared with atorvastatin by the end of the study period (58% vs 37%; $p < 0.001$ vs atorvastatin). In conclusion, CRP was effectively reduced in patients with type 2 diabetes receiving rosuvastatin or atorvastatin, whereas rosuvastatin decreased LDL cholesterol relatively more than atorvastatin.[27]

The use of statins is associated with reduced thrombosis burden and diminished platelet activity, as shown in animal models and in vitro studies. Seventy patients with the metabolic syndrome who were not taking antiplatelet agents were consecutively assigned to one of six statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin) at starting doses or to a no-statin group, at the discretion of the responsible clinician, for a period of 6 weeks. Rosuvastatin and the other statins inhibited the activity and antigen level of the platelet PAR-1 thrombin receptor, which has a major role in regulating platelet activity and thrombin formation.[28]

In managed care, patients at high risk for coronary heart disease participated in a randomized, open-label, multicenter trial (SOLAR [Satisfying Optimal LDL-C ATP III goals with Rosuvastatin]), which was performed at 145 US clinical centers. High-risk men and women in a managed care population received typical starting doses of rosuvastatin (10 mg/day), atorvastatin (10 mg/day), or simvastatin (20 mg/day) for 6 weeks. Those who did not meet the LDL-C target of less than 100 mg/dL at 6 weeks had their dose titrated (doubled), and all patients were followed up for another 6 weeks. A total of 1632 patients were randomized to one of the three treatment regimens. After 12 weeks, 76% of patients taking rosuvastatin reached the LDL-C target of less than 100 mg/dL vs 58% with atorvastatin and 53% with simvastatin. Adverse events were similar for type and frequency in all treatment groups, and only 3% of all patients discontinued treatment because of adverse events. No myopathy was observed, no clinically important impact on renal function was attributed to study medications, and clinically important increases in serum transaminases were rare.[29]

Statin therapy decreases LDL cholesterol levels and the risk of coronary heart disease but has a considerable short-term effect on health care budgets. In the US, the cost effectiveness of rosuvastatin has been compared with those of atorvastatin, pravastatin, and simvastatin in lowering LDL cholesterol levels and achieving NCEP III LDL cholesterol goals. Clinical data were obtained from the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR) trial. Drug costs were based on wholesale acquisition costs. Cost effectiveness was assessed with the net monetary benefit approach and a 1-year time horizon. Rosuvastatin was demonstrated to be the most cost-effective statin.[30]

The new target (LDL cholesterol below 70 mg/dL) indicated by the NCEP III guidelines for patients at high risk of coronary heart disease can be difficult to attain with diet and current therapy. In a 16-week multinational trial, 1993 high-risk patients were randomized to rosuvastatin 20 mg, atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, or simvastatin 40 mg for 8 weeks. Patients either remained on starting treatment or switched to lower or milligram-equivalent doses of rosuvastatin for 8 more weeks. More very high risk patients achieved an LDL-C target of <70 mg/dL when changed to rosuvastatin from atorvastatin or simvastatin.[31]

Patients at risk of coronary heart disease may not achieve recommended LDL cholesterol goals on statin monotherapy. A study was designed to investigate the efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg in patients at high risk of coronary heart disease. Four hundred sixty-nine patients were randomly assigned to rosuvastatin alone or in combination with ezetimibe for 6 weeks. Significantly more patients receiving rosuvastatin/ezetimibe than rosuvastatin alone achieved their ATP III LDL cholesterol goal (<100 mg/dL, 94.0% vs 79.1%) and the optional LDL cholesterol goal (<70 mg/dL) for very high-risk patients (79.6% vs 35.0%). The combination of rosuvastatin/ezetimibe reduced LDL cholesterol significantly more than rosuvastatin (−69.8% vs −57.1%).[32]

Vascular trials

Atherosclerosis is often at an advanced stage when symptoms appear: vascular abnormalities are detectable before overt clinical disease and stabilization of vulnerable plaque is thought to precede reduction in cardiovascular events. Vascular end-points have thus been used to evaluate the impact of lipid-lowering treatment on the vascular system.

Also in the case of rosuvastatin, controlled clinical trials using vascular end-points have been performed.

A study assessed whether statin therapy could slow progression and/or cause regression of carotid intima-media thickness (CIMT) over 2 years in middle-aged individuals with a low Framingham risk score (FRS) and mild to moderate subclinical atherosclerosis. This randomized, double-blind, placebo-controlled study (Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin [METEOR]) of 984 individuals, with either age (mean, 57 years) as the only coronary heart disease risk factor or a 10-year FRS of less than 10%, modest CIMT thickening (1.2–3.5 mm), and elevated LDL cholesterol (mean, 154 mg/dL), was conducted in 61 primary care centers in the United States and Europe. Participants received either a 40-mg dose of rosuvastatin or placebo.

Rate of change in CIMT was assessed by B-mode ultrasound for 12 carotid sites, at the level of the common carotid artery, carotid bulb, and internal carotid artery. Among participants in the rosuvastatin group, the mean baseline LDL cholesterol level of 155 mg/dL declined to 78 mg/dL, with a mean reduction of 49%. The change in maximum CIMT for the 12 carotid sites was −0.0014 mm per year for the rosuvastatin group vs +0.0131 mm per year for the placebo group ($p < 0.001$). In summary, middle-aged adults with an FRS of less than 10% and evidence of subclinical atherosclerosis, taking rosuvastatin, experienced significant reductions in the rate of progression of maximum CIMT over 2 years vs placebo.[33]

To further evaluate the impact of rosuvastatin treatment on carotid atherosclerosis, magnetic resonance imaging (MRI) was used to non-invasively assess changes in atherosclerotic plaque morphology and composition (ORION trial). The randomized, double-blind ORION trial used 1.5-T MRI to image carotid atherosclerotic plaques at baseline and after 24 months of rosuvastatin treatment. Forty-three patients with fasting LDL cholesterol between 100 and 250 mg/dL and 16% to 79% carotid stenosis by duplex ultrasound were randomized to receive either a low (5 mg) or high (40/80 mg) dose of rosuvastatin. In these patients with moderate hypercholesterolemia, rosuvastatin treatment was associated with a reduction in percent of lipid-rich necrotic core, whereas the overall plaque burden remained unchanged over the course of 2 years of treatment.[34] The results of this study and of the previous one support the idea that long term treatment with rosuvastatin stabilizes carotid plaques.

Prior intravascular ultrasound (IVUS) trials have demonstrated slowing or halting of atherosclerosis progression with statin therapy but have not provided convincing evidence of regression using percent atheroma volume, the most rigorous IVUS measure of disease progression and regression. To assess whether very intensive statin therapy could induce regression of coronary atherosclerosis, a prospective, open-label blinded end-points trial (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden [ASTEROID]) was performed at 53 community and tertiary care centers in the United States, Canada, Europe, and Australia.

After 24 months, 349 patients had evaluable serial IVUS examinations. Very high-intensity statin therapy using rosuvastatin 40 mg/day achieved an average LDL-C of 60.8 mg/dL and increased HDL-C by 14.7%, resulting in significant regression of atherosclerosis for all prespecified IVUS measures of disease burden.[35]

In the same study, blinded quantitative coronary angiography analyses of percent diameter stenosis and minimum lumen diameter were performed for up to 10 segments of coronary arteries and major branches with >25% diameter stenosis at baseline. For each patient, the mean of all matched lesions at baseline and study end was calculated. There were 292 patients with 613 matched stenoses.

Rosuvastatin treatment for 24 months to average LDL cholesterol levels well below 70 mg/dL, accompanied by significant increases in HDL cholesterol, produced regression by decreasing percent diameter stenosis and improving minimum lumen diameter as measured by quantitative coronary angiography in coronary disease patients.[36]

On-trial effect of rosuvastatin on glomerular filtration rate (GFR) can be regarded as evidence of therapeutic impact on a micro-vascular end-point.

To better define the effect of short-term rosuvastatin treatment on the estimated glomerular filtration rate (eGFR), the database of controlled clinical trials in the Rosuvastatin Clinical Development Program was reviewed. Thirteen studies comprising 3956 rosuvastatin-treated patients were selected based on a serum creatinine measurement at 6 or 8 weeks after initiation of rosuvastatin treatment, randomization to approved and marketed rosuvastatin doses (5 to 40 mg), and unchanged rosuvastatin dose from treatment initiation (baseline) through 6 to 8 weeks of treatment. eGFR was determined with the Modification of Diet in Renal Disease formula. eGFR significantly increased for each dose of rosuvastatin individually and for all doses combined compared to baseline (range +0.9 to +3.2 mL/min/1.73 m^2). Further analysis of 5 blinded, placebo-controlled trials comprising 525 patients showed an increase in eGFR of +0.8 mL/min/1.73 m^2 for all rosuvastatin-treated patients, which was significantly different from a change of −1.5 mL/min/1.73 m^2 in the placebo-treated patients.

The increase in eGFR for rosuvastatin-treated patients was consistent across all major demographic and clinical subgroups of interest, including patients with baseline proteinuria, baseline eGFR <60 mL/min/1.73 m^2, and in patients with hypertension and/or diabetes. In conclusion, these results are consistent with previous rosuvastatin studies that showed an upward trend in eGFR with long-term treatment.[37]

One possible mechanism underlying the favorable vascular effect of rosuvastatin treatment focuses on improvement of endothelial dysfunction. Elevated plasma levels of asymmetric dimethylarginine (ADMA) have been associated with attenuated endothelium-dependent vasodilation in hypercholesterolemic patients. A multicenter, randomized, double-blind, placebo-controlled study included 46 patients with elevated LDL cholesterol. Patients were randomized into 2 groups: rosuvastatin 10 mg/day and placebo for 6 weeks. Plasma levels of ADMA, 8-isoprostane (as a marker of oxidative stress), homocysteine, and high-sensitivity CRP were measured at baseline and 6 weeks later.

Endothelial function assessed by flow-mediated vasodilation of the brachial artery was performed in 11 patients in the rosuvastatin group and in 12 in the placebo group. Baseline characteristics of both groups were similar, and the plasma ADMA levels were significantly correlated with 8-isoprostane. After 6 weeks of treatment, plasma ADMA levels were significantly reduced in the rosuvastatin group (from 0.60 to 0.49 μmol/L, $p < 0.001$). Increases in flow-mediated vasodilation were positively correlated with reductions in plasma levels of ADMA and LDL cholesterol. Thus, these findings suggest that treatment with rosuvastatin in patients with hypercholesterolemia may lead to a significant reduction in plasma ADMA levels, which appear to be related to the improvement in endothelial function by rosuvastatin.[38]

Secondary prevention

There are overwhelming data in favor of cholesterol as a modifiable risk factor for clinically overt coronary artery disease. In this area, rosuvastatin trials are showing their first, although promising results.[39]

Patients with acute coronary syndrome (ACS) were randomly assigned, before percutaneous coronary intervention (PCI), to either the group of no statin treatment (control group: n = 220, 63 years, male 62%) or the group of 40 mg rosuvastatin loading before PCI (rosuvastatin group: n = 225, 64 years, male 60%). Incidence of periprocedural myocardial injury was assessed by analysis of CK-MB and cardiac troponin T before PCI, at 6 hours and the next morning after PCI. After PCI, incidence of periprocedural myocardial injury was higher in controls than in the rosuvastatin group (11.4% vs 5.8%). Mean preprocedural CK-MB and high sensitivity CRP were similar between the two groups, whereas after PCI, peak values of both markers were significantly higher in controls than in the rosuvastatin group. Multivariate analysis revealed that no prior use of statin, procedural complication and multi-vessel disease were the independent predictors for periprocedural myocardial infarction. Thus, a single high dose of rosuvastatin prior to PCI reduces periprocedural myocardial injury in patients with ACS.[40]

Primary prevention

Considering the limitations of current risk assessment strategies, adjunctive markers are needed to improve the prediction of a first coronary event. Research on the inflammatory nature of atherosclerosis suggests that inflammatory-response proteins may serve as potential predictors of clinical events. One in particular, CRP, has been the focus of much attention. Epidemiologic studies have shown a fairly consistent independent association between high-sensitivity CRP (hs-CRP) elevations and coronary risk, although a causal relation has not yet been established.[41,42]

JUPITER[43] is a randomized, double-blind, placebo-controlled primary prevention trial of statin therapy among persons with average to low levels of LDL cholesterol who are at increased cardiovascular risk due to elevated plasma concentrations of the inflammatory biomarker hs-CRP. A total of 17,802 individuals with LDL cholesterol less than 130 mg/dL (3.36 mmol/L) and hs-CRP above 2 mg/L were recruited from 26 countries and randomly allocated to 20 mg/day rosuvastatin or placebo. In contrast to previous studies of statin therapy in primary prevention, JUPITER evaluated a group with modest plasma concentrations of LDL cholesterol (median 108 mg/dL). Further, the trial included 6801 women (38.2%) and 5577 individuals with metabolic syndrome (32.1%). Most participating patients were overweight or frankly obese.

On March 31, 2008 the decision was announced to stop the JUPITER clinical study early based on a recommendation from an Independent Data Monitoring Board and the JUPITER Steering Committee, which met on March 29, 2008. The study was stopped early (after a median follow-up of approximately 2 years) because there was unequivocal evidence of a reduction in cardiovascular morbidity and mortality among patients who received rosuvastatin when compared to placebo.

Recently the final data of this study have become available.[44] Rosuvastatin reduced LDL cholesterol levels

by 50% and hs-CRP levels by 37%. The rates of the primary end point (combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes) were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; $p < 0.00001$), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; $p = 0.0002$), 0.18 and 0.34 for stroke (hazard ratio, 0.52; $p = 0.002$), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; $p < 0.00001$), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; $p < 0.00001$), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; $p = 0.02$). The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes. In this primary prevention trial on persons without hyperlipidemia but with elevated hs-CRP levels, rosuvastatin significantly reduced the incidence of major cardiovascular events.

Conclusion/expert comment

On the basis of the above data, it can be concluded that rosuvastatin beneficially alters the entire spectrum of lipoprotein particles.

Results of previous randomized trials have shown that interventions able to lower LDL cholesterol concentrations can significantly reduce the incidence of coronary heart disease and other major vascular events in a wide range of individuals. However, each separate trial has limited power to assess specific outcomes or categories of participants. A prospective meta-analysis of data from 90,056 individuals in 14 randomized trials of statins was carried out. Weighted estimates were obtained of the effects on different clinical outcomes per 1.0 mmol/L reduction in LDL cholesterol. Over a mean period of 5 years, 8186 people died, 14,348 had major vascular events, and 5103 developed cancer. Mean LDL cholesterol differences at 1 year ranged from 0.35 mmol/L to 1.77 mmol/L (mean 1.09) in these trials. There was a 12% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol. This reflected a 19% reduction in coronary mortality, and non-significant reductions in non-coronary vascular mortality. There were corresponding reductions in myocardial infarction or coronary death, in the need for coronary revascularisation, and in fatal or non-fatal stroke; combining these, there was a 21% decrease in any such major vascular event. These benefits were significant within the first year, but were greater in subsequent years. There was no evidence that statins increased the incidence of cancer overall or at any particular site.

The proportional reduction in major vascular events differed significantly according to the absolute reduction in LDL cholesterol achieved. Prolonged rosuvastatin treatment, which is associated with substantial LDL cholesterol lowering, is expected to produce pronounced benefit in all patients at high risk of any type of major vascular event.[45]

To determine the extent to which statins reduce serum concentrations of LDL cholesterol and incidence of ischemic heart disease (IHD) events and stroke, according to drug, dose, and duration of treatment, 3 meta-analyses were performed: 164 short term randomized placebo controlled trials of 6 statins and LDL cholesterol reduction; 58 randomized trials of cholesterol lowering by any means and IHD events; and 9 cohort studies and the same 58 trials on stoke. Reductions in LDL cholesterol according to statin and dose and reduction in IHD events and stroke for a specified reduction in LDL cholesterol were calculated. Reductions in LDL cholesterol (in the 164 trials) were 2.8 mmol/L (60%) with rosuvastatin 80 mg/day, 2.6 mmol/L (55%) with atorvastatin 80 mg/day, 1.8 mmol/L (40%) with atorvastatin 10 mg/day, lovastatin 40 mg/day, simvastatin 40 mg/day, or rosuvastatin 5 mg/day, all from pretreatment concentrations of 4.8 mmol/L. Pravastatin and fluvastatin achieved smaller reductions. In the 58 trials, for an LDL cholesterol reduction of 1.0 mmol/L the risk of IHD events was reduced by 11% in the first year of treatment, 24% in the second year, 33% in 3 to 5 years, and by 36% thereafter ($p < 0.001$ for trend). IHD events were reduced by 20%, 31%, and 51% in trials grouped by LDL cholesterol reduction (means 0.5 mmol/L, 1.0 mmol/L, and 1.6 mmol/L). After several years a reduction of 1.8 mmol/L should reduce IHD events by an estimated 61%. Results from the same 58 trials, corroborated by results from the nine cohort studies, show that lowering LDL cholesterol decreases all stroke events by 10% for a 1 mmol/L reduction and by 17% for a 1.8 mmol/L reduction. Rosuvastatin, at its lowest dose (5 mg/day) can lower LDL cholesterol concentration by an average of 1.8 mmol/L which reduces the risk of IHD events by about 60% and stroke by 17%. Even better results are expected after treatment at the commonly used dose of 10 mg/day.[46]

A prospective meta-analysis was performed on data from 18,686 individuals with diabetes (1466 with type 1 and 17,220 with type 2), within the context of a further sample of 71,370 without diabetes in 14 randomized trials of statin therapy. Weighted estimates of the effects on clinical outcomes per 1.0 mmol/L reduction in LDL cholesterol

were obtained. During a mean follow-up of 4.3 years, there were 3247 major vascular events in people with diabetes. There was a 9% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol in participants with diabetes, which was similar to the 13% reduction in those without diabetes. This finding reflected a significant reduction in vascular mortality and no effect on non-vascular mortality in participants with diabetes. There was a significant 21% proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol in people with diabetes, which was similar to the effect observed in those without diabetes. Rosuvastatin (10 mg/day) produces an average reduction of LDL cholesterol above 2.0 mmol/L. Therefore in the case of diabetic individuals who are at sufficiently high risk of vascular events, a reduction of vascular events greater than 50% is expected after long-term rosuvastatin treatment.[47]

Early epidemiological studies have identified low levels of HDL cholesterol (<1.0 mmol/L or 40 mg/dL), a common feature of type 2 diabetes mellitus and the metabolic syndrome, to be an independent determinant of increased cardiovascular risk. The beneficial effects of HDL cholesterol on the cardiovascular system have been attributed to its ability to remove cellular cholesterol, as well as its anti-inflammatory, antioxidant and antithrombotic properties, which act in concert to improve endothelial function and inhibit atherosclerosis, thereby reducing cardiovascular risk. As such, raising HDL cholesterol in patients with aggressively lowered LDL cholesterol provides an additional strategy for addressing the residual cardiovascular risk present in these patients groups. Studies suggest that for every 0.03 mmol/L (1.0 mg/dL) increase in HDL cholesterol, absolute cardiovascular risk is reduced by 2% to 3%, in a 4-year follow-up. Raising HDL cholesterol can be achieved by both lifestyle changes and pharmacological means, the former comprising mainly smoking cessation, aerobic exercise, weight loss and dietary manipulation. Therapeutic strategies to increase HDL cholesterol include niacin, fibrates, thiazolidinediones and bile acid sequestrants.[48]

Rosuvastatin, which produces an increase in HDL cholesterol in the range of 4 to 6 mg/dL, is expected, through this mechanism, to be responsible for an additional cardiovascular risk reduction in the range of 8% to 6%. Support for these new data come from the JUPITER study, which was stopped before the programmed end of the study because of excess benefit for high-risk individuals receiving rosuvastatin treatment.[40] It is suggested that pronounced LDL reduction, in association with significant HDL cholesterol increase, are the bases of a marked preventive action of rosuvastatin. The results from JUPITER support the use of rosuvastatin for primary cardiovascular prevention, in overweight men and women, with near to normal LDL cholesterol and high CRP. There is now evidence of benefit from rosuvastatin treatment for a wide segment of the general population at intermediate cardiovascular risk. In absolute numbers, this segment represents the main source of cardiovascular events.[49] On the basis of JUPITER results, it is expected that treatment target and potential candidates for statin therapy will be revaluated and redefined.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
2. Rosenson RS. Rosuvastatin: a new inhibitor of HMG-coA reductase for the treatment of dyslipidemia. *Exp Rev Cardiovasc Ther*. 2003;1:495–505.
3. McKenney JM. Efficacy and safety of rosuvastatin in treatment of dyslipidemia. *Am J Health Syst Pharm*. 2005;62:1033–1047.
4. SEARCH Collaborative Group, Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy – a genomewide study. *N Engl J Med*. 2008;359:789–799.
5. Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther. 2006;80:565–581.
6. Bottorff MB. Statin safety and drug interactions: clinical implications. *Am J Cardiol*. 2006;97:27C–31C.
7. Schneck DW, Birmingham BK, Zalikowski JA, et al. The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther*. 2004;75:455–463.
8. Simonson SG, Raza A, Martin PD, et al. Rosuvastatin pharmacokinetics in heart transplant recipients administered anantirejection regimen including cyclosporine. *Clin Pharmacol Ther*. 2004;76:167–177.
9. Merz T, Fuller SH. Elevated serum transaminase levels resulting from concomitant use of rosuvastatin and amiodarone. *Am J Health Syst Pharm*. 2007;64:1818–1821.
10. Shepherd J, Hunninghake DB, Stein EA, et al. Safety of rosuvastatin. *Am J Cardiol*. 2004;94:882–888.
11. Jacobson TA. Toward "pain-free" statin prescribing: clinical algorithm for diagnosis and management of myalgia. *Mayo Clin Proc.* 2008;83:687–700.
12. Marie I, Delafenêtre H, Massy N, Thuillez C, Noblet C; Network of the French Pharmacovigilance Centers. Tendinous disorders attributed to statins: a study on ninety-six spontaneous reports in the period 1990–2005 and review of the literature. *Arthritis Rheum*. 2008;59:367–372.
13. Jacobson TA. The safety of aggressive statin therapy: how much can low-density lipoprotein cholesterol be lowered? *Mayo Clin Proc*. 2006;81:1225–1231.
14. LaRosa JC. Low-density lipoprotein cholesterol reduction: the end is more important than the means. *Am J Cardiol*. 2007;100:240–242.
15. McKenney JM. Pharmacologic options for aggressive low-density lipoprotein cholesterol lowering: benefits versus risks. *Am J Cardiol*. 2005;96:60E–66E.
16. Schwartz GG, Bolognese MA, Tremblay BP, et al. Efficacy and safety of rosuvastatin and atorvastatin in patients with hypercholesterolemia and a high risk of coronary heart disease: a randomized,controlled trial. *Am Heart J*. 2004;148:e4.

17. Jones PH, Hunninghake DB, Ferdinand KC, et al; Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin Study Group. Effects of rosuvastatin versus atorvastatin, simvastatin, and pravastatin on non-high-density lipoprotein cholesterol, apolipoproteins, and lipid ratios in patients with hypercholesterolemia: additional results from the STELLAR trial. *Clin Ther*. 2004;26:1388–1399.
18. Ballantyne CM, Raichlen JS, Cain VA. Statin therapy alters the relationship between apolipoprotein B and low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol targets in high-risk patients: the MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin) trial. *J Am Coll Cardiol*. 2008;52:626–632.
19. Schuster H, Barter PJ, Stender S, et al; Effective Reductions in Cholesterol Using Rosuvastatin Therapy I study group. Effects of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I) study. *Am Heart J*. 2004;147:705–713.
20. Stein EA, Strutt K, Southworth H, Diggle PJ, Miller E; HeFH Study Group Comparison of rosuvastatin versus atorvastatin in patients with heterozygous familial hypercholesterolemia. *Am J Cardiol*. 2003;92:1287–1293.
21. Stein EA, Amerena J, Ballantyne CM, et al. Long-term efficacy and safety of rosuvastatin 40 mg in patients with severe hypercholesterolemia. *Am J Cardiol*. 2007;100:1387–1396.
22. Deedwania PC, Hunninghake DB, Bays HE, Jones PH, Cain VA, Blasetto JW; STELLAR Study Group. Effects of rosuvastatin, atorvastatin, simvastatin, and pravastatin on atherogenic dyslipidemia in patients with characteristics of the metabolic syndrome. *Am J Cardiol*. 2005;95:360–366.
23. Ooi EM, Watts GF, Nestel PJ, Sviridov D, Hoang A, Barrett PH. Dose-dependent regulation of high-density lipoprotein metabolism with rosuvastatin in the metabolic syndrome. *J Clin Endocrinol* Metab. 2008;93:430–437.
24. Asztalos BF, Le Maulf F, Dallal GE, et al. Comparison of the effects of high doses of rosuvastatin versus atorvastatin on the subpopulations of high-density lipoproteins. *Am J Cardiol*. 2007;99:681–685.
25. Lamendola C, Abbasi F, Chu JW, et al. Comparative effects of rosuvastatin and gemfibrozil on glucose, insulin, and lipid metabolism in insulin-resistant, nondiabetic patients with combined dyslipidemia. *Am J Cardiol*. 2005;95:189–193.
26. Ai M, Otokozawa S, Asztalos BF, et al. Effects of maximal doses of atorvastatin versus rosuvastatin on small dense low-density lipoprotein cholesterol levels. *Am J Cardiol*. 2008;101:315–318.
27. Betteridge DJ, Gibson JM, Sager PT. Comparison of effectiveness of rosuvastatin versus atorvastatin on the achievement of combined C-reactive protein (<2 mg/L) and low-density lipoprotein cholesterol (<70 mg/dl) targets in patients with type 2 diabetes mellitus (from the ANDROMEDA study). *Am J Cardiol*. 2007;100:1245–1248.
28. Serebruany VL, Miller M, Pokov AN, et al. Effect of statins on platelet PAR-1 thrombin receptor in patients with the metabolic syndrome (from the PAR-1 inhibition by statins [PARIS] study). *Am J Cardiol*. 2006;97:1332–1336.
29. Insull W Jr, Ghali JK, Hassman DR, et al; SOLAR Study Group. Achieving low-density lipoprotein cholesterol goals in high-risk patients in managed care: comparison of rosuvastatin, atorvastatin, and simvastatin in the SOLAR trial. *Mayo Clin Proc*. 2007;82:543–550.
30. Miller PS, Smith DG, Jones P. A Cost effectiveness of rosuvastatin in treating patients to low-density lipoprotein cholesterol goals compared with atorvastatin, pravastatin, and simvastatin (an US Analysis of the STELLAR Trial). *Am J Cardiol*. 2005;95:1314–1319.
31. Ballantyne CM, Bertolami M, Hernandez Garcia HR, et al. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapy (MERCURY) II. *Am Heart J*. 2006;151:975.e1–e9.
32. Ballantyne CM, Weiss R, Moccetti T, et al; EXPLORER Study Investigators; Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). *Am J Cardiol*. 2007;99:673–680.
33. Crouse JR 3rd, Raichlen JS, Riley WA, et al; METEOR Study Group. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA*. 2007;297:1344–1353.
34. Underhill HR, Yuan C, Zhao XQ, et al. Effect of rosuvastatin therapy on carotid plaque morphology and composition in moderately hypercholesterolemic patients: a high-resolution magnetic resonance imaging trial. *Am Heart J*. 2008;155:584.e1–e8.
35. Nissen SE, Nicholls SJ, Sipahi I, et al; ASTEROID Investigators. *JAMA*. 2006;295:1556–1565.
36. Ballantyne CM, Raichlen JS, Nicholls SJ, et al; ASTEROID Investigators. Effect of rosuvastatin therapy on coronary artery stenoses assessed by quantitative coronary angiography: a study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden. *Circulation*. 2008;117:2458–2466.
37. Vidt DG, Harris S, McTaggart F, Ditmarsch M, Sager PT, Sorof JM. Effect of short-term rosuvastatin treatment on estimated glomerular filtration rate. *Am J Cardiol*. 2006;97:1602–1606.
38. Lu TM, Ding YA, Leu HB, Yin WH, Sheu WH, Chu KM. Effect of rosuvastatin on plasma levels of asymmetric Dimethylarginine in patients with hypercholesterolemia. *Am J Cardiol*. 2004;94:157–161.
39. Gotto AM Jr. Review of primary and secondary prevention trials with lovastatin, pravastatin, and simvastatin. *Am J Cardiol*. 2005;96: 34F–38F.
40. Yun KH, Jeong MH, Oh SK, et al. The beneficial effect of high loading dose of rosuvastatin before percutaneous coronary intervention in patients with acute coronary syndrome. *Int J Cardiol*. 2008 Aug 13. [Epub ahead of print].
41. Gotto AM Jr. Role of C-reactive protein in coronary risk reduction: focus on primary prevention. *Am J Cardiol*. 2007;99:718–725.
42. Mora S, Ridker PM. Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) can C-reactive protein be used to target statin therapy in primary prevention? *Am J Cardiol*. 2006;97:33A–341A.
43. Ridker PM, Fonseca FA, Genest J, et al; JUPITER Trial Study Group. Baseline characteristics of participants in the JUPITER trial, a randomized placebo-controlled primary prevention trial of statin therapy among individuals with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein. *Am J Cardiol*. 2007;100:1659–1664.
44. Ridker PM, Danielson E, Fonseca FA, et al; the JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. 1: *N Engl J Med*. 2008;359(2):2195–2207.
45. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
46. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326:1423.
47. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371:117–125.
48. Hausenloy DJ, Yellon DM. Targeting residual cardiovascular risk: raising high-density lipoprotein cholesterol levels. *Heart*. 2008;94:706–714.
49. Rubba P. Orphans of best prevention. *Nutr Metab Cardiovasc Dis*. 2007;17:483–485.