Clinical Medicine Insights: Cardiology

EXPERT REVIEW

Rosuvastatin: A Review of the Pharmacology and Clinical Effectiveness in Cardiovascular Disease

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Abstract: Rosuvastatin is a new generation HMG-CoA reductase inhibitor which exhibits some unique pharmacologic and pharmacokinetic properties. It has low extrahepatic tissue penetration, low potential for CYP3A4 interactions and substantial LDL-C lowering capacity and therefore has distinct advantages. We conducted a Medline literature search to identify rosuvastatin papers published in English. In this review, we outline the pharmacology of rosuvastatin, highlighting its efficacy and safety. We also review the major clinical trials with reference to primary and secondary prevention, familial hypercholesterolaemia and comparison with other statins. Finally we address its place in clinical practice.

Keywords: rosuvastatin, cardiovascular risk, statins, low density lipoprotein cholesterol

Clinical Medicine Insights: Cardiology 2012:6 17–33

doi: 10.4137/CMC.S4324

This article is available from http://www.la-press.com.

Introduction

Ischaemic heart disease (IHD) is the leading cause of mortality worldwide and constitutes a major health burden. According to World Health Organisation (WHO) statistics it accounts for 12.8% of deaths, with stroke and other cerebrovascular disease accounting for a further 10.8%. In the United Kingdom, data from the Health Surveys for England suggest that while mortality may be declining, cardiovascular disease morbidity continues to rise. Epidemiological studies have established a strong correlation between cholesterol and the incidence of cardiovascular disease. The associated morbidity and mortality is positively correlated to low density lipoprotein cholesterol (LDL-C) and inversely related to high density lipoprotein cholesterol (HDL-C).[1,2]

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors that are effective in the reduction of total and LDL cholesterol.[3] A number of large randomized control trials have demonstrated unequivocally that lowering LDL-C particularly with statins reduces the risk of cardiovascular deaths and events.[4] HMG CoA inhibitors have been shown to prevent initial cardiovascular events and subsequent cardiovascular events in ischaemic heart disease patients, irrespective of the cholesterol concentration.[5,6] In addition to the beneficial cholesterol lowering effects, statins improve endothelial function, enhance stability of atherosclerotic plaques, and inhibit inflammatory as well as thrombogenic responses in arterial walls.[7] Furthermore extensive post marketing surveillance has shown that long term statin therapy is generally well tolerated.[8]

The lipid lowering arms of Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed the benefit of statin therapy in primary prevention of cardiovascular events.[9,10] The 4S study was the first study conclusively linking a statin with improved outcomes in patients with coronary heart disease. It established simvastatin as the most common LDL-C lowering treatment for patients with CHD in northern Europe.[11] Subsequently, more studies including results of the Treating to New targets (TNT) trial have shown that intensive lipid lowering (atorvastatin 80 mg) significantly reduces the risk of recurrent cardiovascular events compared to standard lipid lowering (atorvastatin 10 mg) in stable CHD patients.[12] Other clinical trials using various statins have confirmed similar beneficial effects for ameliorating cardiovascular risk in specific groups such as patients with diabetes, heart failure and renal failure. Early detection and treatment with statins has been shown to reduce morbidity and mortality in those with heterozygous familial hypercholesterolaemia.[13]

The reduction in cardiovascular events from statin therapy is proportional to the LDL-C reduction. A 1.0 mmol/L reduction in LDL-C results in a 20% decrease in major coronary events and revascularisation.[14] Larger reductions in LDL-C are associated with greater reductions in cardiovascular events, so more potent statins result in greater cardiovascular risk reduction. The drive towards more stringent goals for LDL-C lowering in cardiovascular risk prevention has brought high impact statin therapy into focus.[12] Different statins have varying effects on LDL-C reduction with rosuvastatin producing the greatest reduction and fluvastatin the least.[15] Statins vary in their lipophilicity and metabolism. These affect their extrahepatic tissue penetration and drug interactions with potential safety implications. Rosuvastatin which is a new generation HMG-CoA reductase inhibitor exhibits some unique pharmacologic and pharmacokinetics properties.[16] It has low extrahepatic tissue penetration, low potential for CYP3A4 interactions and substantial LDL-C lowering capacity and may therefore have some advantages. Its potential impact in primary and secondary prevention of cardiovascular disease in different groups including heart failure, elderly, renal failure and diabetes, and also in combination with other lipid lowering drugs is the subject of ongoing clinical studies.

In this review, we will outline the pharmacology of rosuvastatin; highlight its efficacy and safety. We will also review clinical studies with reference to primary and secondary prevention, familial hypercholesterolaemia and comparison with other statins. Finally we will address its place in clinical practice.

Pharmacology

Rosuvastatin is a fully synthetic HMG-CoA reductase inhibitor. Other HMG-CoA reductase inhibitors are either natural, mevinic acid derived (lovastatin, simvastatin, pravastatin) or synthetic, heptenoic acid derived (atorvastatin, fluvastatin). Rosuvastatin belongs to a

new generation of methane-sulphonamide pyrimidine and *N*-methane sulfonyl pyrrole-substituted 3, 5-dihydroxy-heptenoates. Although the characteristic statin pharmacophore remains similar to other statins, the addition of a stable polar methane-sulphonamide group provides low lipophilicity and enhanced ionic interaction with HMG-CoA reductase enzyme thus improving its binding affinity to this enzyme.[16–18]

Pharmacodynamics

Rosuvastatin competitively inhibits HMG-CoA reductase enzyme selectively and reversibly. This enzyme converts HMG-CoA to mevalonic acid in the cholesterol biosynthetic pathway which is the rate limiting step in cholesterol synthesis. Rosuvastatin therefore decreases hepatic sterol synthesis, which, in turn, leads to a decreased concentration of hepatocellular cholesterol. Hepatocytes respond to this decreased intracellular cholesterol concentration by increased synthesis of LDL receptors to enhance hepatic LDL reuptake from the circulation. The net result of this process is an increased fractional catabolism of LDL which reduces serum LDL-C concentration and total cholesterol.[19,20] Statins also reduce production of ApoB leading to reduced hepatic output of very low density lipoprotein cholesterol (VLDL-C) and triglycerides.[21] In patients with homozygous familial hypercholesterolaemia, rosuvastatin decreases LDL-C despite absence of functional LDL receptors. This may be secondary to marked inhibition of cholesterol synthesis which decreases LDL production. Rosuvastatin has demonstrated comparable reductions in triglyceride (TG) concentrations to other statins with the greatest benefit seen in patients with high baseline TG levels. Studies have shown rosuvastatin to increase HDL-C by 8%–12% with no clear relationship between the dose and response, although the increase is greatest in patients with low baseline HDL-C levels.[22,23] This may be due to reduction of cholesterol ester transfer protein (CETP).[24]

The affinity of rosuvastatin for the active site of the enzyme is four times greater than the affinity of HMG-CoA for the enzyme. It has the highest affinity for HMG-CoA reductase among statins marketed in Europe. This high affinity coupled with tight ionic interaction result in a slow recovery of enzyme activity after removal of rosuvastatin.[25] Since it is a hydrophilic statin, rosuvastatin relies on the organic anion transporting polypeptide-1B1 (OATP-1B1), which is strongly expressed on the hepatocyte basolateral membrane, as the key mechanism for active transport into hepatocytes. Its affinity for OATP-1B1 is comparable to atorvastatin but significantly greater than pravastatin or simvastatin. Rosuvastatin is therefore primarily distributed to hepatocytes while peripheral concentrations are low.[26]

As observed with other statins, rosuvastatin has pleiotropic effects independent of HMG-CoA reductase inhibition. These include improvements in endothelial function, anti-inflammatory, antithrombotic and anti-oxidant effects.[27] Rosuvastatin and other statins improve endothelial function by increasing the production of endothelial nitric oxide and reducing the production of oxygen derived free radicals. This in turn reduces endothelial dysfunction that has been implicated in atherosclerosis. Rosuvastatin reduces high sensitivity C reactive protein (hsCRP) which is a marker of inflammation and an independent cardiovascular risk predictor and other inflammatory markers.[28] Rosuvastatin inhibits platelet aggregation to leukocytes which inhibit formation of clots in injured endothelium.[29]

Pharmacokinetics

The oral bioavailability of rosuvastatin is 20%, which is comparable to atorvastatin, pravastatin and fluvastatin, and qualitatively higher than simvastatin and lovastatin. After a single oral dose the peak plasma concentration is reached at 5 hours. This is longer than other HMG-CoA inhibitors which achieve maximum plasma concentrations in less than 3 hours. In compiled data from pharmacokinetic trials, the peak plasma concentration and area under the concentration time curve show a largely linear relationship as the dose of rosuvastatin increases from 5 to 80 mg. Food intake decreases the rate of absorption of rosuvastatin by 20% but not the extent of absorption. This does not reduce the cholesterol lowering potency; therefore rosuvastatin can be taken with or without food, and in the morning or evening.[16,17,30]

Approximately 90% of rosuvastatin is protein bound mainly to albumin; other statins have approximately 95% protein binding except pravastatin which has a lower protein binding of 50%. The mean volume of distribution is 134 litres in steady state. Rosuvastatin is less lipophilic than other statins such

as atorvastatin and simvastatin but more lipophilic than pravastatin. Penetration of statins into extrahepatic tissues occurs by passive diffusion and is dependent on their lipophilicity. This has implications on their muscle safety as increased rhabdomyolysis was reported in patients on lipophilic agents like cerivastatin and lovastatin.[31,32]

Human hepatocyte studies indicate that rosuvastatin is a poor substrate for metabolism by cytochrome P450 and hence 90% of the drug is excreted unchanged. CYP2C9 is the main isoenzyme involved in metabolism with minimal effect from CYP2C19.[33] Rosuvastatin is metabolised to an N-desmethyl metabolite which is less potent than the parent drug in inhibiting HMG-CoA reductase activity. The parent drug rosuvastatin is responsible for approximately 90% of plasma HMG-CoA inhibitor activity. Rosuvastatin is less likely to cause metabolic drug to drug interactions since it has limited metabolism by CYP isoenzymes. Other HMG-CoA reductase inhibitors such as atorvastatin and simvastatin are metabolised via CYP3A4. Their plasma concentrations are increased by inhibitors of CYP3A4 such as itraconazole, protease inhibitors and macrolide antibiotics.[16,30,33] Table 2 compares the pharmacokinetics of different statins.

Rosuvastatin has a plasma half life of 19 hours which is longer than atorvastatin (15 hours) and simvastatin (2–3 hours). It is primarily eliminated in the faeces (90%) compared with 10% renal excretion. Approximately 72% of absorbed rosuvastatin is eliminated in bile and 28% via renal excretion.[33]

Clinical Trials

There have been a number of clinical studies evaluating rosuvastatin on its own, against placebo and against other statins in various clinical settings.

Rosuvastatin in primary prevention

Clinical studies have demonstrated the benefits of statins in primary prevention. This is believed principally to be secondary to reduction in LDL-C, high sensitivity C-reactive protein (hsCRP) and elevation of HDL-C though other effects are recognised. The Cholesterol Treatment Trialists' Collaborators (CTT) meta-analysis established that a 1 mmol/L reduction in LDL cholesterol results in a 20% reduction in cardiovascular risk.[14] The benefit of statins in low risk populations was demonstrated in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study where reduction of cholesterol using pravastatin 10 mg reduced cardiovascular events by 33%.[35]

JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) marked an important juncture in primary cardiovascular disease prevention with statins. The participants had a mean Framingham risk score at baseline of 11.6% and would otherwise not have qualified for lipid lowering therapy. They were apparently healthy individuals with normal levels of LDL-C (<3.4 mmol/L) and increased hsCRP (>2 mg/L). The hsCRP threshold value of 2 mg/L is the approximate median hsCRP value after 30 days of statin therapy. It originated from secondary prevention trials and in particular the PROVE-IT-TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis In Myocardial Infarction) and A to Z (Aggrastat to Zocor) which showed that achieving this level of hsCRP was associated with improved cardiovascular outcomes.[36] JUPITER was a randomised, double blind, placebo-matched, multicentre trial conducted at 1315 sites in 26 countries. 17,802 participants received either 20 mg of rosuvastatin, or matched placebo, and were followed up every six months. 12 months into the study, the rosuvastatin group had a 50% lower median LDL-C, 37% lower median hsCRP and 17% lower median triglyceride level ($P < 0.001$ for all three comparisons) which persisted to study completion. The observed increase in HDL-C was transient. Results showed that rosuvastatin was associated with a significant reduction in first major cardiovascular events (HR 0.56; 95% CI, 0.46 to 0.69; $P < 0.00001$) which was the primary endpoint. Reductions were further seen in the incidence of the individual components of the trial end point including myocardial infarction (54%), stroke (48%), arterial revascularisation (47%), unstable angina and death from cardiovascular causes. This is important as up to 50% of all myocardial infarctions and strokes occur in patients with LDL cholesterol concentrations that are considered normal.[37] The benefits were largely similar for men and women, and were observed in all subgroups including age, ethnicity, region and cardiovascular risk score.

Table 1. Trial acronyms.

Acronym	Full meaning
AFCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
ALLHAT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ANDROMEDA	A raNdomized, Double-blind, double-dummy, multicentre, phase IIIb, parallel-group study to compare the efficacy and safety of Rosuvastatin (10 mg and 20 mg) and atOrvastatin (10 mg and 20 mg) in patiEnts with type 2 DiAbetes mellitus
ASTEROID	A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-derived Coronary Atheroma Burden
A to Z	Aggrastat to Zocor
AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events
CARDS	Collaborative Atorvastatin Diabetes Study
CENTAURUS	Comparison of the Effects Noted in The ApoB:ApoA-I ratio Using Rosuvastatin or Atorvastatin in Patients with Acute Coronary Syndrome
CORALL	Cholesterol Lowering Effects of Rosuvastatin compared with Atorvastatin in patients with type 2 diabetes
CORONA	Controlled Rosuvastatin Multinational Trial in Heart Failure
COSMOS	Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects
4D	Deutsche Dialyse Diabetes Study
GEOSTAT	Hepatic Metabolism and Transporter Gene Variants Enhance Response to Rosuvastatin in Patients With Acute Myocardial Infarction
GISSI-HF	Gruppo Italiano per lo Studio della Supravvivenza nell'Insufficienza cardiaca
IDEAL	Incremental Decrease in Endpoints through Aggressive Lipid Lowering
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease
MEGA	Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
METEOR	Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin
MIRACL	Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering
ORION	Outcome of Rosuvastatin Treatment on Carotid Artery Atheroma: a Magnetic Resonance Imaging Observation
PLUTO	Paediatric Lipid Reduction Trial of Rosuvastatin
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PULSAR	Prospective Study to Evaluate Low Doses of Atorvastatin and Rosuvastatin
4S	Scandinavian Simvastatin Survival Study
SATURN	Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin
SHARP	Study of Heart and Renal Protection
SPACEROCKET	Secondary Prevention of Acute Coronary Events – Reduction of Cholesterol to Key European Targets Trial
STELLAR	Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses
TNT	Treating to New Targets
URANUS	Use of Rosuvastatin versus Atorvastatin in type 2 diabetes mellitus
WOSCOPS	West of Scotland Coronary Prevention Study

Previously, there has been limited data on statin benefits in women, black and Hispanic patients.

Since the results of JUPITER were initially published, several secondary subgroup analyses of the study population have been reported. Participants with a 10 year low baseline risk (<5%) benefited less than those with risk >5%. Participants with a 10 year intermediate baseline risk by Framingham (5%–20%) experienced incremental absolute risk reductions that were proportional to their global risk.[38] In a different subgroup analysis, participants at high global risk (10 year Framingham score >20%) showed no additional benefit for the combined endpoint of myocardial infarction, stroke and

Table 2. Pharmacokinetics of statins.

Comparative pharmacokinetics of statins							
Parameter	**Rosuvastatin**	**Atorvastatin**	**Simvastatin**	**Pravastatin**	**Fluvastatin**	**Pitavastatin**	**Lovastatin**
T_{max} (h)	3	2–3	1.3–2.4	0.9–1.6	0.4–2.1	0.6–0.8	2–4
Bioavailability	20	12	5	18	24	80	5
Lipophilicity	No	Yes	Yes	No	Yes	Yes	Yes
Protein binding	88	80–90	94–98	43–55	>98	96	95
Metabolism	Minimal CYP2C9 CYP2C19 Biliary excretion	CYP3A4	CYP3A4	Sulfation Biliary & urine excretion	CYP2C9	Minimal CYP2C8 CYP2C9	CYP3A4
Metabolites	Active (minor)	Active	Active	Inactive	Inactive	Active (minor)	Active
$T^1/_2$ (h)	19	15	2–3	1.3–2.8	1.2	10–11	2.9
Urinary excretion	10	2	13	20	6	NA	10
Faecal excretion	90	70	58	71	90	90	83

Note: Data from Soran et al.[34]
Abbreviations: T_{max}, time to peak plasma concentration; $T^1/_2$ (h), half life.

cardiovascular death (HR 0.50; 95% CI, 0.27 to 0.93) when compared with subjects who had an intermediate Framingham risk score.[39]

Another series of sub analyses have looked at lipid profiles and hsCRP particularly in relation to residual cardiovascular risk. In all of them, participants who achieved low concentrations of hsCRP in addition to low values of the lipid parameters of interest had the best outcome. When hsCRP is included in enrolment of primary prevention, rosuvastatin produced greater benefit when compared with other statins.[40]

These results compare favourably with other primary prevention trials using different statins. WOSCOPS (West of Scotland Coronary Prevention Study) showed that pravastatin 40 mg in men with moderate hypercholesterolaemia reduced incidence of myocardial infarction and cardiovascular death by 31%.[41] Similarly, AFCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) demonstrated that lovastatin 20–40 mg daily reduced risk of first major coronary event by 37% in men and women with average LDL-C and below average HDL-C when compared with placebo.[42] In the ASCOT lipid lowering arm, atorvastatin 10 mg reduced the incidence of myocardial infarction, stroke and cardiovascular death by 36% compared to placebo.[9] Figure 1 shows the CHD event reduction in primary prevention trials.

Rosuvastatin in secondary prevention

The beneficial effects of statin therapy in patients with ischaemic heart disease are well known. The 4S study showed that simvastatin 20 mg to 40 mg daily significantly reduced major coronary events, coronary death and overall mortality in patients post-MI or those with ischaemic heart disease.[43] In the LIPID study (Long-term Intervention with Pravastatin in Ischaemic Disease), pravastatin 40 mg reduced cardiovascular events and mortality in patients with history of myocardial infarction or unstable angina with different baseline lipid profiles.[44] Other studies

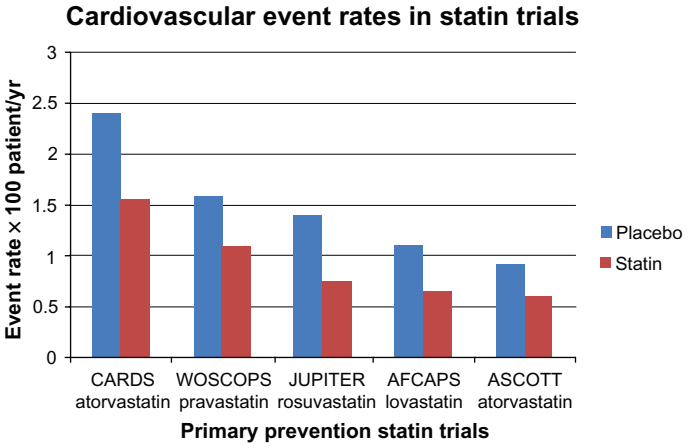

Figure 1. CHD event rate in primary prevention trials.

have also established the benefits of treatment after myocardial infarction.

a) Stable coronary heart disease (CHD)/Arrest and regression of atherosclerosis

The TNT trial comparing atorvastatin 80 mg with atorvastatin 10 mg, investigated whether intensive treatment to achieve LDL-C <1.81 mmol/L was associated with better outcomes. Mean LDL-C of 2 mmol/L was realised with intensive treatment. A relative risk reduction of 22% was achieved for the primary outcome which was the occurrence of a first major cardiovascular event.[12] The IDEAL study (Incremental Decrease in Endpoints through Aggressive Lipid Lowering) compared the effect of atorvastatin 80 mg and simvastatin 20 mg on cardiovascular outcomes. There were significant reductions in non fatal acute myocardial infarction and in other secondary composite endpoints, with no difference in cardiovascular or all-cause mortality. Statistical significance was not demonstrated for the prespecified primary clinical outcome which was time to first occurrence of major coronary event.[45] In as much as there have been no clinical outcome data for secondary prevention with rosuvastatin, a number of studies have compared their effect on surrogate markers and achievement of treatment goals. The STELLAR study (Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses) showed that at different doses, rosuvastatin reduced total cholesterol better than other statins, and triglycerides better than simvastatin and pravastatin. Additionally a larger proportion of rosuvastatin patients achieved National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C targets when compared with atorvastatin.[46,47] PULSAR (Prospective Study to Evaluate Low Doses of Atorvastatin and Rosuvastatin) showed that in hypercholesterolaemic patients with vascular occlusive disease rosuvastatin 10 mg was better than atorvastatin 20 mg at reducing LDL-C, improving other lipid parameters and enabling achievement of US and European treatment goals.[47–49] Table 3 shows current LDL-C treatment targets.

Several studies have suggested that reduction in plaque volume is linked to the clinical outcome. ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-derived Coronary Atheroma Burden) investigated the impact of high dose rosuvastatin on regression of atherosclerosis. The results showed that rosuvastatin 40 mg produced significant reduction in LDL-C (53% from baseline; $P < 0.001$), increase in HDL-C (14.7% from baseline; $P < 0.001$) and regression of atheroma volume in the most diseased coronary arteries in 78% of participants. A median reduction of 6.8% in atheroma volume was recorded by IVUS (intravascular ultrasound). It must be noted that the study was non-comparative and open label.[50] Other studies including ORION (Outcome of Rosuvastatin Treatment on Carotid Artery Atheroma: a Magnetic Resonance Imaging Observation) and METEOR (Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin) demonstrated that rosuvastatin 40 mg achieved a 49% LDL-C reduction and slowed progression of atherosclerosis as assessed by carotid intima-media thickness (CIMT) but did not result in regression of CIMT. The lack of plaque regression may have occurred because low risk patients with minimal subclinical carotid atherosclerosis were used in the study. The COSMOS (Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects) study found that rosuvastatin achieved significant reduction of coronary plaque volume with good safety in stable Japanese CHD patients.[51,52] The recently concluded SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin)

Table 3. Current LDL-C treatment goals.

Guideline	Risk	Target
ESC	Very high risk	<1.8 mmol/L or 50% reduction if target unachievable
	High risk	<2.5 mmol/L
	Moderate risk	<3 mmol/L
JBS 2	High risk	2 mmol/L
NCEP ATP III	CHD	<100 mg/dL (2.6 mmol/L)
	≥2 risk factors	<130 mg/dL (3.4 mmol/L)
	0–1 risk factors	<160 mg/dL (4.2 mmol/L)

Abbreviations: ESC, European Society of Cardiology; JBS 2, Joint British Societies Guidelines on Prevention of Cardiovascular Disease in Clinical Practice; NCEP ATP III, National Cholesterol Education Programme Adult Treatment Panel III.

study compared maximal doses of rosuvastatin and atorvastatin on coronary atheroma. It reported that although rosuvastatin achieved lower LDL-C and higher HDL-C, both agents produced similar percentage reduction in atheroma volume.[53]

b) Acute coronary syndrome (ACS)

The NCEP ATP III guidelines recommend that intensive statin treatment should be used in patients admitted with acute coronary syndrome.[47] The European Society of Cardiology (ESC) and the American College of Cardiology (ACC) have recommended LDL-C levels of 1.8 mmol/L as the optimal target for very high risk patients (established CHD, type I diabetes with end organ damage, moderate to severe chronic kidney disease (CKD) or a SCORE level >10%).[48] Several studies have provided evidence of the additional LDL-C lowering achieved by intensive statin therapy.

The PROVE-IT study found that intensive treatment with atorvastatin 80 mg was better than pravastatin 40 mg at preventing death and major cardiovascular events following ACS.[54] The A to Z study which compared 40 mg and 80 mg of simvastatin demonstrated a benefit which did not reach statistical significance, while the MIRACL (Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering) study showed that early intensive treatment with atorvastatin 80 mg after ACS led to a 16% reduction in death, acute MI, unstable angina and cardiac arrest, compared with placebo.[55] Meta-analyses of intensive statin trials have also shown that intensive treatment provides benefit above lower intensity treatment in prevention of myocardial infarction and strokes in patients with known coronary disease irrespective of the baseline LDL-C. The CENTAURUS (Comparison of the Effects Noted in The ApoB:ApoA-1 ratio Using Rosuvastatin or Atorvastatin in Patients with Acute Coronary Syndrome) study showed that 20 mg rosuvastatin produced similar changes in ApoB:ApoA-1 ratio at 3 months when compared with atorvastatin 80 mg. Previous studies have identified ApoB:ApoA-1 ratio as an important predictor of myocardial infarction. In the same study rosuvastatin 20 mg achieved similar LDL-C reduction as atorvastatin 80 mg. This study therefore showed that rosuvastatin 20 mg is as effective as atorvastatin 80 mg in intensive statin therapy.[56] In SPACEROCKET (Secondary Prevention of Acute Coronary Events—Reduction of Cholesterol to Key European Targets Trial), a larger proportion of patients on rosuvastatin 10 mg achieved ESC, ACC and American Heart Association (AHA) optimal LDL-C target of less than 1.81 mmol/L when compared to those on simvastatin 40 mg. A crucial observation of this study was that in both treatment arms, most patients did not achieve these targets, highlighting the importance of intensive statin therapy to meet these goals. The superior lipid lowering effect of rosuvastatin makes it a good candidate for intensive lipid lowering.[57]

Rosuvastatin in women

Previous primary prevention trials have poorly demonstrated reduction in coronary events in women. In JUPITER the relative risk reduction in the primary end point and overall mortality was similar in men and women. Although women benefited more than men with regard to revascularisation/unstable angina, no significant benefit was seen for myocardial infarction, stroke or death from cardiovascular causes.[58]

Rosuvastatin in the elderly

Randomised control trial (RCT) data are limited regarding statin efficacy in the elderly. 5695 participants from JUPITER were >70 years at recruitment. They accounted for 49% of the confirmed primary end points in the trial. Analysis of this group showed an absolute risk reduction of the primary end point 48% greater than that observed in younger subjects. There were no serious safety concerns raised for this age group compared with younger subjects.[59]

Rosuvastatin in renal disease

Advanced kidney disease is associated with high cardiovascular morbidity and death. RCT evidence has shown an inconsistent relationship between cardiovascular outcome and LDL-C in haemodialysis patients. WOSCOPS showed benefit only in mild stages of CKD (eGFR > 60 mL/min per 1.73 m^2). In JUPITER, participants with moderate CKD benefited as much as those with preserved renal function in terms of primary end point reduction and faired better for all-cause mortality.[60]

AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular

Events) investigated the effects of rosuvastatin on cardiovascular risk in haemodialysis patients. It was a randomised, double blind, placebo-matched, multicentre trial involving 2776 patients aged 60–80 years. Good median reductions were achieved in LDL-C (42.9%), total cholesterol (26.6%), triglycerides (16.2%) and hsCRP (11.5%). Despite these reductions, there was no significant effect of treatment on the composite primary end point (time to a major cardiovascular event) or its individual components (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes). This lack of efficacy was seen in all prespecified subgroups including diabetes, known CHD, hypertension, elevated hsCRP and high HDL-C. Thus, no relationship was demonstrated between cardiovascular end points and either baseline or follow up LDL-C. A further evaluation of secondary outcomes showed no reduction in all-cause mortality or non-cardiovascular death.[61] Similar results have been obtained from the 4D study which looked at atorvastatin.[62] In contrast to these studies, the SHARP (Study of Heart and Renal Protection) study which compared a combination of simvastatin 20 mg and ezetimibe 10 mg to placebo, found 17% reduction in major atherosclerotic events per 0.85 mmol/L reduction in LDL-C in CKD patients.[63] The implication of these findings is that some of the cardiovascular morbidity and mortality in haemodialysis patients may not be mediated by atherogenic processes.

Rosuvastatin in diabetes

Type 2 diabetes is associated with increased risk of coronary heart disease. In the UK Prospective Diabetes Study (UKPDS), every 1 mmol/L increment in LDL-C was associated with a 57% increase in relative risk of coronary heart disease. Furthermore, the LDL-C of diabetic patients predicted their risk of stroke.[64] CARDS (Collaborative Atorvastatin Diabetes Study) showed that atorvastatin 10 mg led to a reduction in cardiovascular events and strokes in diabetes patients without high HDL-C and no prior history of cardiovascular disease.[65] This has strengthened the need for statin therapy for primary prevention in diabetes patients. Sub-group analyses of 4S showed the benefits of simvastatin in reducing major coronary events and revascularisation in diabetic patients with coronary heart disease. However, the reduction in total and cardiovascular mortality was not significant due to the small sample size.[66]

A randomised double blind double-dummy, multicentre, phase IIIb, parallel-group study to compare the efficacy and safety of rosuvastatin (10 mg and 20 mg), and atorvastatin (10 mg and 20 mg) in patients with type 2 diabetes mellitus (ANDROMEDA) showed that rosuvastatin produced greater reductions in LDL-C, ApoB and total cholesterol when compared with equal doses of atorvastatin. A greater proportion of patients on rosuvastatin achieved European LDL-C goals compared to those on atorvastatin.[67] The CORALL (Cholesterol Lowering Effects of Rosuvastatin compared with Atorvastatin in patients with type 2 diabetes) study showed that rosuvastatin produced greater reductions in ApoB:ApoA-1 ratios, LDL-C and total cholesterol in diabetic patients with moderate dyslipidaemia.[68] The superior effect of rosuvastatin compared with atorvastatin in reduction of LDL-C was also demonstrated in the URANUS (Use of Rosuvastatin versus Atorvastatin in type 2 diabetes mellitus) study.[69]

Familial hypercholesterolaemia (FH)

Many FH guidelines recommend a >50% reduction of LDL-C in heterozygous FH. Studies comparing different lipid lowering regimens demonstrate that only high impact therapy with rosuvastatin 40 mg or atorvastatin 80 mg achieves this goal when administered as monotherapy.[70] In all other circumstances, combination therapy with ezetimibe, bile acid sequestrants, fibrates, nicotinic acid or fish oils is often required.[71] There are no randomised control trial (RCT) outcome data with these combinations in FH. Whereas it is accepted that LDL apheresis and plasmapheresis are suitable treatments for homozygous FH, there are no RCTs comparing LDL apheresis and drug treatment alone. The use of LDL apheresis in heterozygous FH patients is thus unclear and at present maximal drug therapy is the preferred treatment.

Rosuvastatin in heart failure

The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) investigated the effect of rosuvastatin 10 mg in patients with New York Heart Association functional class II-IV systolic heart failure from ischaemic heart disease. The CORONA study did not establish any reduction in composite

cardiovascular outcome and death despite favourable effects on LDL-C, triglycerides, HDL-C and CRP. The use of rosuvastatin did however reduce hospitalisation from cardiovascular causes.[72] A similar trend was found in the GISSI-HF study in which only 40% of patients had ischaemic heart failure. In the GISSI HF (Gruppo Italiano per lo Studio della Supravvivenza nell'Insufficienza cardiac) study, rosuvastatin 10 mg had no effects on primary and secondary endpoints when compared with placebo.[73] The two studies show that rosuvastatin did not have extra benefit in reduction of cardiovascular mortality in patients with ischaemic and non-ischaemic heart failure.

Rosuvastatin in children

Studies in children with heterozygous FH have shown the safety and efficacy of statins, including their effect on carotid intima thickness and arterial flow mediated dilation.[74] PLUTO (Paediatric Lipid Reduction Trial of Rosuvastatin) investigated the efficacy and safety of incremental doses of rosuvastatin in achieving LDL-C treatment targets of <110 md/dL (2.87 mmol/L). A daily dose of rosuvastatin 5, 10 and 20 mg lowered LDL-C by 38, 45 and 50% respectively, with 40% of participants achieving the target. 68% of participants achieved the less stringent goal of LDL-C <130 mg/dL (3.4 mmol/L). This is far better than the adult FH population in who only 22% and 37% will achieve this LDL-C on 20 and 40 mg of rosuvastatin respectively. The effects on other lipid parameters and safety were consistent with other statin studies in adults and children.[75]

Stroke

JUPITER showed a 51% reduction in ischaemic stroke with rosuvastatin, though no beneficial effects were observed for transient ischaemic attacks or haemorrhagic strokes. These benefits were present in all patient groups including women, non smokers and other low risk patients. There was a 39% relative risk reduction of stroke per 1 mmol/L reduction in LDL-C. The beneficial effects were most marked for those who achieved LDL-C <1.8 mmol/L and hsCRP <2 mg/L.[40] Previous studies with other statins such as WOSCOPS and MEGA did not show significant reduction in stroke.[41,35] Rosuvastatin not only reduces the risk of stroke as shown in JUPITER but also slows the rate of progression of carotid atherosclerosis as observed in the ORION and METEOR studies.[51] There has not been any study investigating the effect of rosuvastatin in the secondary prevention of strokes in patients with previous history of stroke. The SPARCL study showed that intensive statin therapy with atorvastatin 80 mg daily resulted in significant reduction in recurrent stroke.[76] A secondary analysis of the SPARCL study found that the effect was greater in patients with established carotid stenosis at baseline. Intensive therapy with rosuvastatin may yield similar benefits.

Highly Active Antiretroviral Therapy (HAART)

HIV patients on highly active antiretroviral therapy are increasingly found to have hypercholesterolaemia and hypertriglyceridaemia. Prospective studies have also shown that these patients have increased incidence of cardiovascular events.[77] Current guidelines recommend statins to treat dyslipidaemia in HIV patients on HAART. Since 90% of rosuvastatin is excreted unchanged in bile with only 10% metabolised by CYP2C9 and CYP2C19, rosuvastatin has minimal drug–drug interactions with most antiretroviral drugs metabolised by CYP3A4.[78]

Protease inhibitors such as ritonavir, saquinavir and atazanavir inhibit OATP-1B1 the transporter protein involved in the hepatic cell uptake of rosuvastatin. This leads to higher serum rosuvastatin concentrations in patients taking protease inhibitors. It is recommended that lower doses of rosuvastatin are used in patients taking protease inhibitors. There are no known drug interactions between rosuvastatin and non nucleoside reverse transcriptase inhibitors (NNRTIs).[79]

A large retrospective cohort study in America found that rosuvastatin produced the largest reduction in LDL-C, non-HDL-C and triglycerides when compared with atorvastatin and pravastatin. It also produced the highest proportion of patients achieving target LDL and non-HDL-C without a difference in toxicity profile when compared with atorvastatin and pravastatin.[80] The British HIV association recommend the use of rosuvastatin in patients receiving HAART.[77]

Safety

In the pooled safety data of controlled Phase II/II trials, the incidence of adverse events during rosuvastatin therapy was comparable to those of other statins.

Subsequent meta-analysis of clinical trials and post marketing experience have consistently shown that rosuvastatin has a comparable safety profile to other available statins when used at 10 mg to 40 mg daily dose.[8] In JUPITER, hepatic injury, myopathy and cancer did not occur more frequently with rosuvastatin than with placebo, despite the fact that LDL-C < 55 mg/dL (1.4 mmol/L) were achieved in half of the rosuvastatin group.[40] AURORA reported a high incidence of adverse and serious adverse events which is consistent with previous studies in haemodialysis patients.[61]

A recent large prospective cohort study of primary care patients from 368 general practices in England and Wales reported findings from 225,922 patients who commenced statin therapy between 2002 and 2008. There were no clinically significant associations between any statins and Parkinson's disease, rheumatoid arthritis, venous thromboembolism, dementia, osteoporotic fracture, gastric cancer, lung cancer, melanoma, renal cancer, breast cancer and prostate cancer. The study further showed that with the exception of fluvastatin, all statins were associated with a dose dependent increased risk of myopathy. A direct comparison test between the individual statins did not yield a significant difference in men ($P = 0.57$) or women ($P = 0.61$). All statins were associated with a dose dependent increased risk of liver dysfunction. The highest risk was associated with fluvastatin while pravastatin and rosuvastatin had the lowest risks. Table 4 shows the hazard ratios of developing myopathy or liver dysfunction with different statins.

Rosuvastatin at every prescribed dose compared favourably with other statins with regard to liver dysfunction, myopathy, cataract, oesophageal cancer and acute renal failure.[81] A meta-analysis of randomised controlled trials on statins showed that there was a positive association between statins and the incidence of diabetes. The combined data reported a 0.39% absolute risk of developing diabetes with 4 years of statin therapy. The risk was higher in older participants of the statin trials. The absolute risk of developing diabetes was 0.6% with rosuvastatin (JUPITER, CORONA), 0.4% with atorvastatin (ASCOT-LLA) and 0.3% for simvastatin (4S). Paradoxically, there was a reduced incidence of diabetes with pravastatin (WOSCOPS, LIPID). It therefore appears that the risk of developing diabetes is marginally higher with rosuvastatin compared to other statins.[82] Other studies that involved rosuvastatin such as JUPITER, CORONA and GISSI HF all had an increased incidence of diabetes in the patients receiving rosuvastatin compared to placebo.[40,72,73] The overwhelming benefit of statins in the reduction of cardiovascular events outweighs the small risk of developing diabetes therefore statin therapy should be used in patients with high cardiovascular risk. All statins can cause myopathy and rhabdomyolysis especially at higher doses. Combination of statins with other medications may lead to increased risk if these medication increase plasma concentrations of the statins. Cases of rhabdomyolysis have been report in patients on medications which increase plasma concentrations of rosuvastatin such as gemfibrozil, liponavir and ritonavir. Table 5 shows drugs which can interact with rosuvastatin.

One unique effect of rosuvastatin is the dose dependent transient proximal isolated low-molecular-weight

Table 4. Adverse outcomes of statins.

Adverse outcomes	Statin	Hazard ratio ♀ (95% CI)	Hazard ratio ♂ (95% CI)
Moderate/severe myopathy	None	1.00	1.00
	Simvastatin	3.30 (2.32–4.69)	6.11 (4.79–7.80)
	Atorvastatin	2.62 (1.42–4.84)	8.18 (5.82–11.50)
	Fluvastatin	Insufficient data	1.20 (0.17–8.53)
	Pravastatin	2.68 (0.99–7.25)	5.79 (3.07–10.91)
	Rosuvastatin	5.41 (2.64–11.07)	4.19 (1.86–9.45)
Moderate/severe liver dysfunction	None	1.00	1.00
	Simvastatin	1.62 (1.41–1.86)	1.79 (160–2.01)
	Atorvastatin	2.00 (1.64–2.44)	1.86 (1.55–2.24)
	Fluvastatin	3.08 (2.14–4.43)	2.37 (1.66–3.38)
	Pravastatin	1.91 (1.37–2.65)	1.13 (0.78–1.62)
	Rosuvastatin	1.31 (0.87–1.97)	1.46 (1.01–2.11)

Data from Hippisley-Cox et al.[81]

Table 5. Rosuvastatin drug interactions.

Drugs that increase plasma concentrations of rosuvastatin
Drugs that antagonise organic anion transporting polypeptide 1B1
Gemfibrozil
Protease inhibitors: ritonavir, liponavir
Cyclosporin
Drugs that reduce plasma concentrations of rosuvastatin
Antacids
Erythromycin
Drugs affected by co-administration with rosuvastatin
Warfarin increased INR
Ethinyl oestradiol: increased concentrations

proteinuria which appears to have no effect on glomerular function.

Efficacy

The STELLAR study showed the greater efficacy of rosuvastatin in improving LDL-C, triglycerides and HDL-C. It is the most effective statin at increasing HDL-C and has a positive effect on apolipoprotein and lipid ratios. Most of the lipid modifying benefit observed in the study was achieved at a 10 mg daily dose.[46] PULSAR compared the efficacy and safety of rosuvastatin 10 mg with atorvastatin 20 mg in high risk patients with vascular occlusive disease. Rosuvastatin 10 mg was better than atorvastatin 20 mg at improving LDL-C, HDL-C, triglycerides and ApoB/ApoA-1 ratio. It also enabled a greater proportion of treated patients to NCEP ATP III and ESC goals.[49] Table 6 compares the efficacy of different statins.

Intermittent rosuvastatin

Several small studies have reported that alternate-day therapy with rosuvastatin has important benefits in addition to improving the lipid profile. These include limitation of adverse reactions, enhanced patient compliance and reduced cost of treatment.[83] Other studies have looked at weekly rosuvastatin for patients with previous statin intolerance. One study achieved reductions of 23% in LDL-C, 17% in total cholesterol, 12% in triglycerides and an increase of 5% in HDL-C in patients who had a prior history of adverse reactions to one or more statins.[84] These alternative dosing regimens have not been proven to reduce cardiovascular risk. A few studies have started reporting the effects of pulsed combination drug therapy involving rosuvastatin in their regimens.[85]

Combination therapy

Very high risk patients or those with severe dyslipidaemia often require combination therapy to achieve treatment goals and enhance lipid profile modification. In one study combination of rosuvastatin 5 mg to 20 mg with fenofibric acid demonstrated significant efficacy in lowering triglycerides and increasing HDL-C when compared with rosuvastatin alone. Furthermore the combination of rosuvastatin with fenofibric acid was well tolerated and as safe as each drug used as monotherapy.[86] Similar results were found by Durrington when combination of rosuvastatin and fenofibrate was used in type 2 diabetes.[87] Further clinical trials are required to establish the benefits in clinical outcomes of combination of rosuvastatin with fenofibrate. The use of rosuvastatin 40 mg with fenofibric acid or fenofibrate has not been evaluated and should therefore not be prescribed routinely.[88] Several studies have shown the efficacy and safety of rosuvastatin in combination with ezetimibe, bile acid sequestrants and fish oils.[89,90] Some small trials and angiographic studies have demonstrated some benefit

Table 6. Efficacy of statins.

Comparative efficacy of statins						
% LDL-C reduction	**Rosuvastatin**	**Atorvastatin**	**Simvastatin**	**Pravastatin**	**Fluvastatin**	**Lovastatin**
<25	5	10	5	10–20	20	10–20
25–35	5	10	10–20	20–40	40–80	20–40
35–45	5–10	10–20	20–40	80		80
45–55	10–20	20–40	80			
55–60	20–40	80				
60–65	40–80					

Data from White.[16]

from combination therapy though this has not been corroborated by randomised clinical trial data.

Cost effectiveness

Economic evaluations show that intensive lipid lowering is a cost effective treatment for very high risk patients groups including those with ACS, heterozygous FH and diabetes. For these purposes, rosuvastatin 40 mg daily was the most optimal treatment based on 2009 prices for statins, providing generic atorvastatin 80 mg was not available.[91] A similar observation was made for lower treatment doses in the PULSAR trial. At the time of the study (2006), annual acquisition costs were lower for rosuvastatin 10 mg than atorvastatin 20 mg in the UK and the US.[49] Our group demonstrated in the GEOSTAT (Hepatic Metabolism and Transporter Gene Variants Enhance Response to Rosuvastatin in Patients With Acute Myocardial Infarction) study that patients with CYP3A5 and/or BCRP variant genotypes who were treated with rosuvastatin achieved treatment targets more frequently than those on simvastatin 40 mg. These results indicate the potential value of genetic profiling of patients to optimise statin response in a cost effective manner.[92]

Place in Therapy

Rosuvastatin is a potent statin with pharmacologic and pharmacokinetic advantages. Its high affinity for OATP-1B1 ensure a high hepatocyte concentration which results in superior efficacy at lowering LDL-C and TG as well as improving HDL-C and ApoB:ApoA-1 ratio compared to other statins. A possible exception is pitavastatin. Rosuvastatin is synthetic with a relatively low lipophilicity when compared with other statins and has minimal entry into peripheral cells. This, coupled with its minimal CYP450 metabolism confers relatively better tolerability, safety and drug interaction profile. As the circulating half life is 19 hrs it can be taken once daily at any time of the day regardless of meals.

Clinical trial data and post marketing surveillance have demonstrated important information about rosuvastatin. Several cardiovascular outcome studies have confirmed the beneficial effects that had been anticipated from vascular imaging studies. JUPITER showed the reduction in cardiovascular events and all cause mortality of rosuvastatin in primary prevention in patients with lower cardiovascular risk. This is the only statin that has been shown to reduce cardiovascular and all cause mortality.[40] Some authors believe that some of the benefits may have been exaggerated by the short duration of the study. Comparative studies have shown the potential benefits of rosuvastatin in secondary prevention and high intensity therapy.[46,49] The long term and legacy effects of rosuvastatin on cardiovascular mortality are awaited. A small increase in diabetes among those >65 years has been observed in rosuvastatin trials, but this occurs with other statins with the exception of pravastatin.[78] Physicians should be aware of the risk of proteinuria in patients on rosuvastatin and should screen for this. Given its potency and safety, rosuvastatin is a versatile statin that can be used in different clinical contexts.

Patients with a 10 year cardiovascular risk of >20% require intensive treatment to achieve LDL-C <2 mmol/L or a >50% reduction from baseline. These include patients with established CHD, moderate to severe CKD, type 1 and type 2 diabetes. Only rosuvastatin 20 mg–40 mg and atorvastatin 80 mg achieve this reduction as monotherapy. A large proportion of these patients are on multiple drug therapy and thus it is crucial to limit pill burden and avoid drug interactions. Most lipid therapy is now aimed at achieving treatment goals from guideline bodies such as ESC, JBS and NCEP ATP III. A new category of patients is thus created by those who fail to achieve these goals with various treatments. Such patients should be considered for treatment with rosuvastatin.

Special groups

Patients with hereditary hyperlipidaemia, particularly FH and FCH should be considered for early treatment with rosuvastatin. Their baseline LDL-C is invariably too high for less potent statins to reduce adequately. Furthermore these patients are at extremely high cardiovascular risk. Patients on HAART should be considered for treatment with rosuvastatin whenever their treatment allows. In this patient group, choice is often limited and determined by the anti-retroviral regimen. They are also at very high cardiovascular risk. Certain patient groups such as those with renal failure and the elderly are at increased risk of statin related myopathy and rhabdomyolysis. Because of its potency, rosuvastatin can be used at very low doses. A number of reports are emerging about intermittent or pulsed therapy which is better tolerated yet

maintains reasonable lipid control. As with other potent statins, lower doses of rosuvastatin should be used in patients from South East Asia to reduce risk of rhabdomyolysis.

In conclusion rosuvastatin is an effective and safe statin which is ideal second line treatment for most patients requiring primary or secondary prevention. When there is a history of previous statin intolerance or multiple drug therapy, low dose rosuvastatin may be considered. For patient groups at very high risk where stringent LDL-C reduction is envisaged, rosuvastatin should be considered as a potential first line treatment. Its benefits against cost in patients with lower cardiovascular risk remain an issue of debate.

Abbreviations

ACC, American College of Cardiology; ACS, Acute coronary syndrome; AHA, American Heart Association; Apo A-1, Apolipoprotein A-1; ApoB, Apolipoprotein B; BCRP, Breast cancer resistance protein; CHD, Coronary heart disease; CYP3A4, Cytochrome P450 3A4; CETP, Cholesterol ester transfer protein; CYP2C9, Cytochrome P450 2C9; CYP2C19, Cytochrome P450 2C19; CIMT, Carotid intima media thickness; CKD, Chronic kidney disease; CRP, C-reactive protein; CYP3A5, Cytochrome P450 3A5; CYP450, Cytochrome P450 mixed function oxidase system; ESC, European Society of Cardiology; FCH, Familial combined hypercholesterolaemia; FH, Familial hypercholesterolaemia; HAART, Highly active antiretroviral therapy; HDL-C, High density lipoprotein cholesterol; HIV, Human immunodeficiency virus; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; hsCRP, High sensitivity C-reactive protein; IVUS, Intravascular ultrasound; JBS, Joint British Societies; LDL-C, Low density lipoprotein cholesterol; NCEP ATP III, National Cholesterol Education Programme Adult Treatment Panel III; NNRTI, Non nucleoside reverse transcriptase inhibitors; OATP-1B1, Organic anion transporting polypeptide 1B1; RCT, Randomised control trial; TG, Triglycerides; VLDL-C, Very low density lipoprotein cholesterol; WHO, World Health Organisation.

Declaration of Interest

JHB and ASH were investigator and principal investigator for the SPACEROCKET study which was funded by an unrestricted educational grant and both have received honoraria for speaking at AstraZeneca sponsored meetings. ASH has received fees consulting for AstraZeneca. No fee has been received for preparation of the manuscript.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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