EXPERT OPINION

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Rosuvastatin calcium in acute coronary syndromes

Rajesh K Aggarwal† & Refai Showkathali
Basildon University Hospital, Essex Cardiothoracic Centre, Cardiology, Basildon, UK

Introduction: Low-density lipoprotein cholesterol (LDL-C) reduction using 3-hydroxy-3-methyl glutaryl coenzyme A (HMGCoA) reductase inhibitors (statins) has a proven survival benefit in patients presenting with acute coronary syndromes (ACS). Patients presenting with ACS remain at significant risk of subsequent cardiovascular death and non-fatal myocardial infarction despite high compliance with current guideline indicated secondary prevention therapies. There remains, therefore, a need to consider the potential benefits of more intensive LDL-C lowering after presentation with ACS. Rosuvastatin is the most potent of the currently available statins and has some unique pharmacological properties that may be advantageous in such patients.

Areas covered: We conducted a Medline literature search to identify rosuvastatin papers and papers on statin use in ACS published in English. In this review, we outline the pharmacology of rosuvastatin and examine its efficacy and safety. We also evaluate the published trials of statin therapy in ACS and offer an opinion on the use of rosuvastatin in ACS.

Expert opinion: There is adequate clinical trial evidence confirming the LDL-C lowering efficacy and safety of high-dose rosuvastatin in ACS. Whilst there are sound theoretical reasons to consider early use of high-dose rosuvastatin in ACS, the available level of evidence is insufficient to justify a wholesale change from the current standard of care.

Keywords: acute coronary syndromes, rosuvastatin, secondary prevention, statins

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1. Introduction

Coronary artery disease remains the single most frequent cause of death worldwide; in 2008, an estimated 7.3 million deaths worldwide were because of coronary heart disease (CHD) [1]. Amongst patients with CHD, presentation with acute coronary syndromes (ACS; acute myocardial infarction with or without ECG evidence of ST-segment elevation and unstable angina) is associated with high mortality and morbidity [2-4]. The management of ACS has been well characterised and significant reductions in mortality achieved with advances in treatment, in particular, prompt coronary revascularisation and pharmacological therapy aimed at reducing early as well as longer term risk [5-8]. An increase in adherence to guidelines and prescription of evidence-based therapies has led to significant reduction in early mortality after hospitalisation for ACS [9]. Nevertheless, patients presenting with ACS remain at significant risk of subsequent cardiovascular death and non-fatal myocardial infarction. Amongst secondary prevention therapies, lipid-lowering therapies, particularly statins (3-hydroxy-3-methyl glutaryl coenzyme A [HMGCoA] reductase inhibitors) play a key role with guidelines advocating the early and continued use of a high-dose statin in all patients without a contraindication or a history of intolerance [5-8]. Whilst use of lipid-lowering drugs has increased substantially in European countries between 1997 and 2006, studies during this period continue to show suboptimal control of lipid levels in patients with established CHD [9-11]. There remains, therefore, a need to prescribe more effective lipid-lowering therapy in such patients. Rosuvastatin

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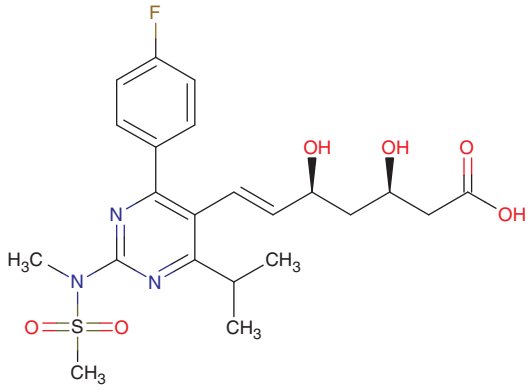
Box 1. Drug summary.

Drug name	Rosuvastatin
Phase	III
Indication	Acute coronary syndromes
Pharmacology description	HMGCoA reductase inhibitor
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	[64,70-72]

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(**Box 1**) is a new generation statin. It is a fully synthetic HMGCoA reductase inhibitor and is the most potent of the currently available statins and has some unique pharmacological properties [12,13]. Its use may, therefore, be advantageous in achieving treatment targets and thus improving outcomes in patients presenting with ACS. In this review, we outline the pharmacology of rosuvastatin and examine its safety and efficacy; we also evaluate the trials of statin therapy in ACS and offer an opinion on the use of rosuvastatin in ACS.

2. Pharmacology of rosuvastatin

Rosuvastatin calcium is the only fully synthetic HMG-CoA reductase inhibitor available. It consists of a single enantiomer formulated and administered as the calcium salt of the active hydroxy acid [14]. As with all statins, the molecule contains an HMG-like moiety that binds to the catalytic domain of the target enzyme, HMG-CoA reductase. The dihydroxyheptanoic acid portion of the molecule is the characteristic statin pharmacophore. In addition, rosuvastatin contains a polar methylsulfonamide group that reduces lipophilicity and enhances interaction with HMG-CoA reductase enzyme [15]. Consequently, of all the statins, rosuvastatin has the greatest number of binding interactions with the active enzyme site and, like atorvastatin, has an additional interaction with the enzyme that is not seen with the other synthetic statins. This additional interaction may partially explain why rosuvastatin is associated with greater lowering of low-density lipoprotein cholesterol (LDL-C) than that achieved with other statins [16].

Rosuvastatin is a competitive, selective and reversible inhibitor of the enzyme HMG-CoA reductase that converts HMG-CoA to mevalonic acid; this is the rate-limiting step in cholesterol biosynthesis. Inhibition of the conversion of HMG-CoA to mevalonate results in the reduction of hepatic biosynthesis of very low-density lipoprotein (VLDL), which leads to decreased numbers of circulating VLDL and LDL particles as well as increased expression of hepatic LDL receptors. The net result of this process is an increased fractional catabolism of LDL, which reduces both serum LDL-C concentration and total cholesterol [15,17].

2.1 Pharmacokinetics

Rosuvastatin achieves peak plasma concentration approximately 5 h after oral administration in humans. At steady state, both peak plasma concentration (C_{max}) and the area under the curve (AUC) have been shown to increase in an almost linear relationship with doses from 5 to 80 mg and there is little or no accumulation (80 mg is not an approved dose of rosuvastatin) [18]. Rosuvastatin has the longest terminal half-life of available statins at approximately 19 h. This extended half-life compared with other statins may explain, in part, the superior efficacy rosuvastatin in lowering LDL-C. This longer half-life also allows administration of rosuvastatin at any time during the day; other statins, except atorvastatin, must be administered late in the day or at bedtime for maximum lipid-lowering efficacy [16]. The absolute bioavailability of rosuvastatin after a single oral dose is approximately 20%. The drug is 88% reversibly bound to plasma proteins, primarily albumin [19]. Other statins have approximately 95% protein binding, except pravastatin which has a lower protein binding of 50%. Rosuvastatin is cleared hepatically by Cytochrome P450 (CYP) 2C9 and 2C19, and this route of elimination is considered to be quite

minor as only 10% of a radiolabelled oral dose is recovered as metabolite and 90% of the drug is eliminated unchanged in the faeces [20]. This may be the reason why the pharmocokinetics of rosuvastatin are unaffected in patients with mild-to-moderate hepatic impairment [21]. The major metabolite of rosuvastatin is approximately 50% less active than the parent compound [22]. Because of its limited metabolism, rosuvastatin may have a low potential for clinically important pharmacokinetic interactions, such as CYP enzyme inhibitors as evidenced by a published series of studies [23-25].

3. Efficacy of statins

The clinical effectiveness of statins in a wide variety of patient groups has been established in numerous randomised clinical trials of both primary (WOSCOPS, AFCAPS/TexCAPS) and secondary (4S,LIPID,TNT,HPS) prevention [26-31]. Prospective meta-analysis of data from more than 90,000 individuals enrolled in 14 randomised clinical trials has shown an approximately 20% risk reduction in all cause mortality, myocardial infarction, need for coronary revascularisation or stroke for each mmol/l reduction of LDL-C irrespective of initial lipid profile or other characteristics [32]. Unsurprisingly, absolute risk reduction is highest in those with the highest baseline risk and those who achieve the greatest reduction in LDL-C. It would seem logical, therefore, that patients presenting with ACS, who constitute a high risk group, would be best served by intensive reduction in LDL-C. The incidence of serious side effects related to statin therapy is low and does not appear to be significantly different amongst the currently available statins [32,33].

3.1 Efficacy of rosuvastatin

3.1.1 Lipid lowering

A large number of studies have evaluated the effect of rosuvastatin on lipid parameters in a range of patients with different lipid disorders. In these studies, rosuvastatin has been observed to lower levels of LDL-C by 45 – 63% and triglycerides by 10 – 35% and to elevate HDL-C by 8 – 14% [22,34]. Rosuvastatin is significantly more potent with regard to LDL-C lowering than the other available statins. Analysis of pooled data from three comparative studies of rosuvastatin and atorvastatin showed that rosuvastatin 10 mg reduced the LDL-C significantly more than atorvastatin 10 mg (47 vs. 36%), simvastatin 20 mg (49 vs. 37%) or pravastatin 20 mg (49 vs. 28%) [35,36]. In a large randomised assessment (STELLAR trial), rosuvastatin has also been shown to lower total cholesterol and raise HDL-C more than atorvastatin, simvastatin and pravastatin with similar levels of tolerability [37]. Guideline-recommended treatment targets are also more likely to be achieved with rosuvastatin than other statins [35-37].

3.1.2 Effects on atherosclerosis

The effects of rosuvastatin on atherosclerosis have been evaluated using both ultrasound and magnetic resonance imaging (MRI) in carotid arteries and using intravascular ultrasound (IVUS) in coronary arteries. In the METEOR study, asymptomatic middle-aged individuals with a low risk of cardiovascular disease, randomly assigned to treatment with rosuvastatin 40 mg daily had a significantly lower rate of progression of maximum carotid intima-media thickness (CIMT) compared with those receiving placebo [38]. A smaller randomised trial (ORION) used high-resolution MRI to evaluate the effects of rosuvastatin 5 mg or 40/80 mg on carotid atheroma in patients with hypercholesterolaemia and asymptomatic carotid disease. This study showed that high-dose rosuvastatin achieved a 59.9% LDL-C reduction and slowed progression of atherosclerosis as assessed by CIMT but did not result in regression of CIMT [39]. The lack of plaque regression may have occurred because low-risk patients with minimal subclinical carotid atherosclerosis were used in the study.

Rosuvastatin is the first statin that has demonstrated the ability to reduce coronary artery atheroma and regress atherosclerosis in a major clinical study, as visualised by IVUS. The ASTEROID study investigated the impact of high-dose rosuvastatin on regression of atherosclerosis [40]. In this open label, non-comparative study, rosuvastatin 40 mg produced significant reduction in LDL-C (53.2% from baseline), increase in HDL-C (14.7% from baseline) 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. The conclusions drawn from this study may be limited by the absence of a control group that would have allowed assessment of the natural progression of atherosclerosis. In addition, of the 158 patients who did not complete the study, 22 were specifically withdrawn because of ischaemic events that may have represented disease progression. In order to investigate any potential bias that their withdrawal may have introduced to the results, the investigators performed exploratory analyses imputing less favorable IVUS outcomes for these patients; the results of these analyses did not alter the conclusions of the trial [40]. A similar open-label noncomparative study in Japanese subjects with hypercholesterolaemia and stable CHD (COSMOS) used IVUS to determine the effect of 76 weeks of rosuvastatin treatment at lower doses (2.5 – 20 mg) on progression of plaque volume. This study found that rosuvastatin achieved significant reduction of coronary plaque volume with a good safety profile [41].

A much larger randomised trial (SATURN) compared the effects of two intensive statin regimes (rosuvastatin 40 mg vs. atorvastatin 80 mg) on the progression of coronary artery disease using serial intravascular ultrasonography in 1039 patients with angiographically proven coronary disease (20 – ≤ 50% stenosis). The primary efficacy endpoint, a surrogate for atheroma regression, was change in percent atheroma volume (PAV). Both agents were well tolerated. After 2 years of therapy the rosuvastatin group had significantly lower LDL-C and significantly higher HDL-C than the atorvastatin group. Both agents induced atherosclerosis regression in the majority of patients: 63.2% with atorvastatin and 68.5% with rosuvastatin for PAV and 64.7 and 71.3%,

respectively, for total atheroma volume (TAV). The PAV reduction, although somewhat greater with rosuvastatin than atorvastatin (1.22 vs. 0.99%), did not differ significantly between the two groups [42].

3.1.3 *Clinical outcomes*

A number of trials evaluating clinically meaningful endpoints using rosuvastatin in a variety of clinical settings have been published. The largest and arguably most impressive of these was the JUPITER study [43]. JUPITER was the first prospective study to evaluate the use of statins in treating patients with normal LDL-C (< 130 mg/dl) but elevated high-sensitivity C-reactive protein (hs-CRP). This large multicentre primary prevention trial enrolled 17,802 apparently healthy people (men aged 50 years or older and women aged 60 years or older) who had LDL-C < 130 mg/dl and hs-CRP ≥ 2.0 mg/l. Participants with chronic inflammatory conditions were excluded from the study. Study subjects were randomly assigned to 20 mg of rosuvastatin daily or placebo and were followed up for the occurrence of the combined primary endpoint of myocardial infarction, stroke, arterial revascularisation, hospitalisation for unstable angina or death from cardiovascular causes. The trial was terminated early after a median follow-up of 1.9 years because of the marked superiority of rosuvastatin compared with placebo. Treatment with rosuvastatin was associated with significant improvement in the composite primary endpoint, as well as each individual component of the primary composite endpoint with the exception of hospitalisation for unstable angina. Rosuvastatin treatment was noted to be associated with an increase in physician-reported new onset diabetes [43]. A subsequent prospective analysis of the JUPITER findings confirmed that the greatest reduction in the primary endpoint was in the treatment group that achieved both LDL-C < 70 mg/dl and hs-CRP < 2 mg/l (65% reduction) compared with only a 33% reduction in patients who achieved only one of these targets [44].

Two clinical endpoint trials using rosuvastatin in different settings have failed to show a significant treatment benefit. In the CORONA study, 5011 patients aged 60 years or older with ischaemic systolic heart failure and New York Heart Association Class II – IV symptoms were randomly assigned to treatment with rosuvastatin 10 mg daily or placebo. Whilst rosuvastatin was associated with significant reductions in LDL cholesterol and hs-CRP, during a median follow-up of 32.8 months it failed to improve the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. Rosuvastatin treatment was associated with a reduction in the pre-specified secondary endpoint of hospitalisation for cardiovascular causes. This lack of benefit cannot be clearly explained [45].

In the AURORA trial, 2776 men and women aged 50 – 80 years who had been receiving regular haemodialysis for at least 3 months were randomly assigned to treatment with either rosuvastatin 10 mg daily or matching placebo. Despite significant median reductions in LDL-C (42.9%), total cholesterol (26.6%), triglycerides (16.2%) and hs-CRP (11.5%) at 3 months, there was no significant treatment effect on the composite primary end point (death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke) or its individual components [46]. This result is concordant with trials of other statins in haemodialysis patients and may reflect differences in the pathogenesis of adverse cardiovascular outcomes amongst patients with end-stage renal disease compared with individuals with normal or less severe renal dysfunction [47,48].

4. Statins in acute coronary syndromes

4.1 Early intensive therapy with statins

The role of statin therapy in secondary prevention for CHD was first established in trials where statin therapy was initiated 3 – 6 months, or longer, after acute MI. Data from observational or small randomised studies published more than a decade ago came to differing conclusions about the utility of early intensive lipid-lowering after ACS [49-51]. However increasing evidence of the possible mechanistic benefits of statins such as plaque stabilisation, reversal of endothelial dysfunction, decreased thrombogenicity and reduced inflammation led to a number of clinical end point trials of early intensive statin therapy in patients presenting with ACS [52,53]. A number of such trials have demonstrated significant benefit with intensive statin therapy after an ACS event (**Table 1**). The MIRACL study was the first randomised controlled study of statin therapy in ACS patients. This study showed that aggressive cholesterol lowering with atorvastatin 80 mg initiated between 24 and 96 h after hospital admission for ACS resulted in a 2.6% absolute reduction and a 16% relative reduction in the primary combined end point of death, nonfatal MI, cardiac arrest with resuscitation or worsening symptomatic myocardial ischemia with objective evidence and emergency rehospitalisation [54]. Although mortality was not reduced significantly in the intensive therapy group, the trial was not powered to detect differences between treatment groups in the individual components of the primary composite end point.

In the PROVE-IT trial, patients hospitalised for ACS were randomised to receive either intensive lipid lowering with 80 mg/day of atorvasatin or moderate lipid lowering with 40 mg/day of pravastatin within 10 days of admission. Intensive lipid lowering was associated with a 16% reduction in the primary composite endpoint (death from any cause, myocardial infarction, documented unstable angina requiring rehospitalisation and revascularisation more than 30 days after randomisation and stroke). Intensive therapy with high-dose atorvastatin had a consistent beneficial effect on cardiac events, including a significant 29% reduction in the risk of recurrent unstable angina and a 14% reduction in the need for revascularisation. The reduction in the rate of death from any cause was of borderline significance (28%, p = 0.07). The benefit of high-dose statin was seen in all patients irrespective of their baseline LDL levels in this study [55]. Furthermore, the

Table 1. Summary of trials of statin use in ACS.

Trial	N (Adults ≥ 18 years)	Drug	Comparator	Endpoint	Duration	Outcome
MIRACL [54]	3086	Atorvastatin 80 mg	Placebo	Death/MI/cardiac arrest/recurrent ischaemia	16 weeks	2.6% ARR with atorvastatin treatment (p = 0.048)
PROVE-IT [55]	4162	Pravastatin 40 mg	Atorvastatin 80 mg	Death/MI/unstable angina requiring hospitalisation/ revascularisation/ stroke	18 – 36 months	3.9% ARR favouring atorvastatin (p = 0.005)
PCI PROVE-IT [56]	2868	Pravastatin 40 mg	Atorvastatin 80 mg	Death/MI/unstable angina requiring hospitalisation/ revascularisation/ stroke	18 – 36 months	5.0% ARR favouring atorvastatin (p = 0.002)
ARMYDA-ACS [58]	171	Atorvastatin 80 mg 12-h pre-procedure + further 40 mg 2 h pre-procedure	Placebo	Death/MI/TVR	30 days	12% ARR with Atorvastatin treatment (p = 0.004)
LUNAR [64]	825	Rosuvastatin 20 mg Rosuvastatin 40 mg	Atorvastatin 80 mg	LDL-C lowering, average over 6 – 12 weeks	6 – 12 weeks	Rosuvastatin 20 mg equivalent to Atorvastatin 80 mg; Rosuvastatin 40 mg superior to Atorvastatin 80 mg
CENTAURUS [65]	753	Rosuvastatin 20 mg	Atorvastatin 80 mg	ApoB:ApoA1 ratio	3 months	No significant difference
SPACEROCKET [66]	1263	Rosuvastatin 10 mg	Simvastatin 40 mg	ESC03 lipid-lowering targets	3 months	No significant difference
Yun *et al.* [70]	445	Rosuvastatin 40 mg pre-procedure	Placebo	PMI, 30-day MACE	30 days	5.6% ARR in PMI (p < 0.05); 9.2% ARR in 30-day MACE (p = 0.002) with rosuvastatin treatment
Yun *et al.* [71]	445	Rosuvastatin 40 mg pre-procedure	Placebo	12-month MACE	12 months	10.7% ARR with rosuvastatin treatment (p = 0.002)
Gao *et al.* [72]	117 (women only)	Rosuvastatin 20 mg loading 12-h pre-procedure and 10 mg 2 h pre-procedure	Placebo	MACE at 3 months MACE at 6 months	6 months	10.4% ARR at 3 months (p = 0.026); 13.9% ARR at 6 months (p = 0.014) with rosuvastatin treatment

Trial acronyms and abbreviations detailed in Table 2.
ARR: Absolute risk reduction; MACE: Major adverse cardiovascular events; PMI: Periprocedural myocardial injury.

PCI-PROVE IT sub-study demonstrated that intensive therapy with 80 mg of atorvastatin, initiated after percutaneous coronary intervention (PCI) for ACS, reduced the incidence of major adverse coronary events significantly compared with 40 mg of pravastatin (21.5 vs. 26.5%, hazard ratio 0.78, p = 0.002) [56]. Intensive statin therapy also reduced the risk of hospitalisation for heart failure after an ACS [57].

Pretreatment with intensive lipid-lowering therapy has also been shown to improve outcomes in ACS patients undergoing PCI. In the ARMYDA-ACS trial, patients with non-ST-segment

Table 2. List of trial acronyms and abbreviations used.

4S	Scandinavian Simvastatin survival study
ACS	Acute coronary syndrome(s)
AFCAPS/TexCAPS	Airforce/Texas coronary atherosclerosis prevention study
Apo	Apolipoprotein
ARMYDA-ACS	Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention [58]
ASCOT-LLA	Anglo-Scandinavian cardiac outcomes Trial lipid lowering arm [79]
ASTEROID Trial	Effect of very high-intensity statin therapy on regression of coronary atherosclerosis
AUC	Area under the curve
AURORA	Rosuvastatin and cardiovascular events in patients undergoing haemodialysis [46]
CENTAURUS	Comparison of the efficacy of rosuvastatin versus atorvastatin in reducing apolipoprotein B/ apolipoprotein A-1 ratio in patients with acute coronary syndrome [65]
CHD	Coronary heart disease
CIMT	Carotid intima-media thickness
C_{max}	Peak plasma concentration
CORONA	Rosuvastatin in older patients with systolic heart failure [45]
COSMOS	Effect of rosuvastatin on coronary atheroma in stable coronary artery disease [41]
CYP	Cytochrome P450
DSCT	Dual-source computed tomography
ECG	Electrocardiogram
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HMGCoA	3-Hydroxy-3-methyl glutaryl coenzyme A
HPS	Heart protection study
hs-CRP	High-sensitivity C-reactive protein
IVUS	Intravascular ultrasound
JUPITER Trial	Justification for the use of statins in primary prevention: an intervention trial evaluating rosuvastatin
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LIPID	Long-term intervention with pravastatin in ischaemic disease study
LRCP	Lipid-rich coronary plaque
LUNAR study	Comparison of lipid-modifying efficacy of rosuvastatin versus atorvastatin in patients with acute coronary syndrome [64]
MACE	Major adverse cardiovascular events
METEOR Trial	Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis [38]
MI	Myocardial infarction
MIRACL	Effects of atorvastatin on early recurrent ischaemic events in acute coronary syndromes [54]
MRI	Magnetic resonance imaging
NSTEACS	Non ST-elevation acute coronary syndrome(s)
ORION	Effect of rosuvastatin therapy on carotid plaque morphology and composition in moderately hypercholesterolemic patients: a high-resolution magnetic resonance imaging trial [39]
PAV	Percent atheroma volume
PCI	Percutaneous coronary intervention
PPCI	Primary percutaneous coronary intervention
PROVE-IT	Intensive versus moderate lipid lowering with statins after acute coronary syndromes [55]
SATURN Trial	Effect of two intensive statin regimens on progression of coronary disease [42]
SPACEROCKET	Secondary prevention of acute coronary events – reduction of cholesterol to key European targets trial
STELLAR Trial	Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses
TAV	Total atheroma volume
TNT	Treating to new targets study
VLDL	Very low-density lipoprotein
WOSCOPS	West of Scotland coronary prevention study

elevation ACS (NSTEACS) were randomised to pre-treatment with atorvastatin (80 mg 12 h before PCI, with a further 40 mg preprocedure dose) or placebo. All patients received long-term atorvastatin treatment thereafter (40 mg/day). The primary end point of the trial (30-day incidence of major adverse cardiac events defined as death, myocardial infarction or unplanned revascularisation) occurred in significantly fewer (5%) of patients in the atorvastatin arm compared with those in the placebo arm (17%), driven primarily by reduction in myocardial infarction. A multivariate analysis revealed that pre-treatment with atorvastatin conferred an 88% risk reduction of 30-day major adverse cardiac events [58].

4.2 Rosuvastatin in acute coronary syndromes

The primary pathophysiologic event in ACS is thought to be plaque rupture followed by thrombus formation. Although the precise mechanisms and factors predisposing to plaque rupture are incompletely understood, the association between ACS and elevated serum concentrations of inflammatory markers such as CRP and IL-6 suggests that chronic inflammation of the coronary arterial wall may play an important role [59-61]. The observation that statin therapy reduces serum inflammatory markers, which are correlated with cardiovascular risk, suggests that the immunomodulatory effects of statin therapy may be an important aspect of the risk reduction achieved with these agents [62]. Rosuvastatin has been shown to exert rapid anti-inflammatory effects in a small trial of 35 patients presenting with troponin-positive ACS; compared with placebo, rosuvastatin (20 mg) treatment significantly reduced the plasma concentration of pro-inflammatory cytokines (IL-6, TNF-α and IFN-γ) at 72 h [63].

Lipid modification using rosuvastatin in patients presenting with ACS has been shown to be safe and effective. In the LUNAR study, once-daily regimens of 20 mg of rosuvastatin, 40 mg of rosuvastatin or 80 mg of atorvastatin were compared for efficacy in reducing low-density lipoprotein (LDL) cholesterol levels in patients with ACS. Mean reduction from baseline in LDL cholesterol averaged over 6 and 12 weeks of treatment was significantly greater with rosuvastatin 40 mg (46.8%) than with atorvastatin 80 mg (42.7%). Increases in HDL cholesterol were significantly greater with rosuvastatin 40 mg (11.9%) and rosuvastatin 20 mg (9.7%) than with atorvastatin 80 mg (5.6%). Rosuvastatin 40 mg was also significantly more effective than atorvastatin 80 mg in improving most other secondary efficacy variables such as total cholesterol, triglycerides and non-HDL cholesterol. Although the incidence of adverse effects was high, it did not differ significantly between the three treatment arms and only a minority of reported adverse events were considered by the investigators to be related to study treatment [64].

The CENTAURUS study compared the efficacy of rosuvastatin 20 mg versus atorvastatin 80 mg in reducing the apolipoprotein B/apolipoprotein A-1 (apoB/apoA-1) ratio at 3 months in 753 patients presenting with NSTEACS in a randomised double-blind, parallel group trial. Although the reduction in apoB:apoA-1 ratio at 1 month was superior using rosuvastatin 20 mg (44.4%) compared with atorvastatin 80 mg (42.9%), the trial failed to meet its primary endpoint as the reduction in apoB:apoA-1 ratio at 3 months was identical (44.4%) [65]. In any case, the relative value of the decrease in the apoB:apoA-1 ratio and LDL-C concentration in the evaluation of statin efficacy is unclear and although the apoB:apoA-1 ratio may be an important predictor of acute myocardial infarction, it is not routinely used as a treatment goal in clinical practice [5-7].

In the SPACEROCKET trial, 1263 patients were randomised within 2 weeks of presentation with acute myocardial infarction in an open label, blinded endpoint study to treatment with either rosuvastatin 10 mg or simvastatin 40 mg. The primary endpoint of the trial, the proportion of patients meeting European Society of Cardiology 2003 (ESC03) lipid treatment targets at 3 months was not significantly different between the two treatment arms. However, rosuvastatin 10 mg lowered the mean cholesterol more effectively than simvastatin and achieved better results for more stringent treatment targets that were in force by the time the study was completed [66]. The genetic substudy from this trial showed that the LDL cholesterol target was achieved more frequently for the one in three patients with CYP3A5 and/or BCRP variant genotypes when prescribed rosuvastatin 10 mg, compared with simvastatin 40 mg, suggesting rosuvastatin use in clinical practice could be better targeted in the future [67].

The reductions in LDL-C using rosuvastatin therapy commenced within 48 h of emergent PCI in ACS patients have also been shown in a small Japanese study to be associated with changes in plaque burden and tissue characteristics of non-culprit coronary plaque after 6 months of treatment using IVUS techniques. There was a significant reduction in overall plaque burden and the lipid volume of plaques in this study [68]. Similar findings using dual-source computed tomography (DSCT) have been shown in another small Japanese study of 11 consecutive patients who had emergent PCI within 24 h of presenting with ACS. A total of 13 lipid-rich coronary plaques (LRCPs) were serially evaluated using DSCT before and 24 weeks after rosuvastatin treatment (2.5 – 5 mg daily, titrated to 10 mg if necessary to achieve a target LDL-C level $\leq$ 80 mg/dl). Although there was no change in post-treatment minimal lumen diameter, lumen volume or longitudinal length of LRCPs, the ratio of lipid core volume to plaque volume significantly decreased as did the remodeling index of target LRCPs [69].

Trials evaluating clinically meaningful endpoints with use of rosuvastatin in acute coronary syndrome have also been published. A Korean study evaluated the use of single high-dose rosuvastatin loading on the outcome of patients with ACS undergoing PCI. An important inclusion criterion for this study was that patients were statin naïve at the time of presentation with ACS. A total of 445 patients were randomised to either no treatment (control group) or rosuvastatin loading (40 mg) before PCI. The primary end point was the occurrence of periprocedural myocardial injury defined as a post-procedural increase of CK-MB to more than twice the normal upper limit in patients with normal baseline enzyme levels. In patients with elevated baseline levels of CK-MB, periprocedural myocardial injury was defined as a subsequent increase of more than 2-fold in CK-MB from baseline value and an additional increase in a second sample. Myocardial infarction by CK-MB elevation more than two times upper normal limit was detected after PCI in significantly more (11.4%) of patients in the control group than those in the rosuvastatin loading group (5.8%). Moreover, the incidence of post-procedural elevation of troponin T was higher in the control group than in the rosuvastatin group. Also of note was that, after rosuvastatin

40 mg loading, hs-CRP levels were significantly less elevated than in the control group (4.8 ± 8.5 mg/dl vs. 16.2 ± 28.1 mg/dl) on the day after PCI. Patients who received rosuvastatin loading before PCI had a lower incidence of 30-day MACE compared with the control group (15.9 vs. 6.7%, p = 0.002). There were no serious side effects associated with rosuvastatin loading. Myalgia without elevation of muscle enzyme occurred in only one patient. Thus, this study showed that high-dose rosuvastatin loading before PCI for patients with ACS is associated with the reduction of periprocedural myonecrosis and inflammatory response [70].

Longer term efficacy of this strategy of single loading dose of rosuvastatin before PCI was confirmed in a subsequent publication relating to the same patients. During 11 ± 3 months of follow-up, MACE occurred in 20.5% of patients in the control group and 9.8% of patients in the rosuvastatin group (p = 0.002). The incidence of death and non-fatal MI was significantly greater in the control group than in the rosuvastatin group (hazard ratio, 3.71; p = 0.021). Multivariate analysis showed that rosuvastatin loading was an independent predictor of reduction in the risk of MACE at 12 months (odds ratio 0.5, p = 0.006). Thus, ACS patients subjected to early revascularisation by PCI had significantly better 12-month outcomes when they received a single 40 mg loading dose of rosuvastatin before PCI [71].

Women presenting with ACS have a higher risk of MACE than men and are generally underrepresented in clinical trials. The efficacy of high-dose rosuvastatin loading before PCI was evaluated in a Chinese study of 117 consecutive female patients presenting with NSTEACS. Patients underwent PCI within 48 h of presentation and were randomly assigned to either rosuvastatin loading (loading dose group – 20 mg rosuvastatin given a mean of 12 h before coronary angiography, with a further 10 mg dose 2 h before procedure) or placebo (control group). The primary end points, 3-month and 6-month incidence of MACE (defined as cardiac death, myocardial infarction or target vessel revascularisation) were met. Three months after PCI, MACE occurred in 1.69% of patients in the loading dose group and 12.07% of those in control group (p = 0.026); at 6 months the incidence was 3.39% in the loading dose group and 17.24% in the control group (p = 0.014). In addition to the improved 3- and 6-month clinical outcomes in this study, rosuvastatin loading was also associated with a significant reduction in periprocedural myocardial injury (evidenced by smaller rises in CK-MB and Troponin I) and periprocedural inflammatory cytokine release (significantly lower increases in serum hs-CRP, IL-1, IL-6 and TNF-α) [72].

5. Safety and tolerability of rosuvastatin

The safety of rosuvastatin has been well established from clinical trials. Meta-analysis of clinical trials and post-marketing surveillance confirm that rosuvastatin at doses of 10 – 40 mg daily has a comparable safety profile to other marketed statins [73,74]. In the JUPITER trial, hepatic injury, myopathy and cancer occurred no more frequently with rosuvastatin than with placebo despite LDL-C levels < 1.4 mmol/l being attained in almost half the rosuvastatin-treated subjects [43]. The AURORA trial reported a high incidence of adverse and serious adverse events in patients taking rosuvastatin compared with placebo, an observation not dissimilar to other stain trials in patients with advanced renal disease [46-48]. Rosuvastatin uniquely is associated with a dose-dependent transient low-molecular-weight proteinuria; however in a meta-analysis of 16 randomised trials enrolling 24,194 subjects, the effects of rosuvastatin and atorvastatin on glomerular filtration rate (GFR) were similarly beneficial, whereas atorvastatin was more effective than rosuvastatin at reducing proteinuria [75].

Myopathy is a rare, but well-recognised potential complication of statin therapy. There were no observed cases of myopathy in the more than 2400 patients in the STELLAR trial [37]. A more recent publication on the adverse effects associated with rosuvastatin reported myalgias in 2.5 – 10% of patients receiving rosuvasatin 5 – 80 mg/day [76]. Seven cases of rhabdomyolysis were observed amongst 1,574 (0.4%) patients taking rosuvastatin 80 mg daily, a dose that is presently neither recommended nor approved for use [76,22].

In clinical trials of rosuvastatin 5 – 40 mg, the frequency of persistent elevations in alanine aminotransferase (ALT) (defined as a 3-fold or greater elevation above the upper normal limit on two separate occasions) was 0.1% or less, a value comparable with that reported for other statins. As with other statins, rosuvastatin-associated elevations in ALT were generally mild and transient and no patient described any accompanying symptoms. A large prospective cohort study of more than 225,000 statin-treated patients across 368 primary care practices in England and Wales found that all statins were associated with a dose-dependent increased risk of hepatic dysfunction. All statins were also associated with a dose-dependent increased risk of myopathy, acute renal failure and cataract. No significant differences were evident between individual statins in either men or women with respect to the incidence of these adverse effects [77].

An additional observation from the JUPITER study involved an increase in rate of newly diagnosed diabetes mellitus in the rosuvastatin-treated group, consistent with findings from other statin studies. In a recently reported meta-analysis of 13 statin trials with 91,140 participants, statin use was associated with a 9% increased risk for incident diabetes. It was also suggested that older participants may have the highest risk of developing diabetes with statins [78]. The absolute risk of developing diabetes was 0.6% with rosuvastatin (JUPITER and CORONA), 0.4% with atorvastatin (ASCOT-LLA) and 0.3% for simvastatin (4S) [28,43,45,79]. There appeared to be a reduced incidence of diabetes with pravastatin (WOSCOPS,LIPID) [26,29]. Thus, the risk of developing diabetes may be marginally higher with rosuvastatin than other statins [78]. Notwithstanding the small increased risk of diabetes associated with statin therapy, the cardiovascular benefits of rosuvastatin and all other statins are likely to greatly outweigh this risk.

6. Conclusion

Statins have transformed the management of cardiovascular disease with incontrovertible evidence of their benefits. Numerous well-conducted clinical trials show the efficacy of these agents in lipid lowering, atherosclerosis regression and meaningful clinical endpoints. Rosuvastatin is a fully synthetic statin with a number of distinct pharmacological properties. It is the most potent of the currently marketed statins with substantial data from well-conducted clinical trials providing evidence to support its use in both primary and secondary prevention. Rosuvastatin is well tolerated and indeed may be tolerated at low doses when other statins are not [80]. Whilst head-to-head randomised trials provide evidence of the superiority of rosuvastatin in lowering LDL-C and achieving treatment targets compared with other commonly prescribed statins, there are no large head-to-head clinical endpoint trials that would mandate its routine and widespread use in clinical practice, particularly in light of the wealth of available evidence to support the use of older statins that are now available as generic formulations.

7. Expert opinion

Rosuvastatin is the most potent of the currently marketed statins with some unique pharmacological properties; theoretically, early intensive lipid lowering after presentation with ACS with high doses of this drug should offer incremental risk reduction in such high-risk patients. There are a number of trials with surrogate end points which strongly suggest that this is indeed the case. Rosuvastatin also raises HDL-C more than other statins which should, theoretically, be beneficial but there is, thus far, no clear evidence from end point trials that this confers incremental benefit to patients. Cardiologists have become accustomed to evidence from large randomised clinical trials showing reductions in clinically meaningful hard endpoints (death, myocardial infarction, stroke and unplanned revascularisation) and such a trial has not been conducted with rosuvastatin in the setting of ACS. The standard of care for lipid lowering in most cardiac centres for ACS patients remains atorvastatin prescribed early at a dose of 80 mg daily; a head-to-head clinical trial of high-dose atorvastatin versus high-dose rosuvastatin evaluating clinically meaningful hard endpoints in the setting of ACS would be most interesting but is unlikely ever to be done given the large numbers of patients that would be needed to prove any net incremental benefit. Even if one were to extrapolate from the mechanistic rosuvastatin trials with surrogate endpoints and use mathematical modeling to elucidate the incremental benefit of using high-dose rosuvastatin in place of high-dose atorvastatin, the additional cost of such a wholesale change would be unjustified now that generic atorvastatin is widely available [81,82]. Given the widespread usage, clinical evidence and excellent safety profile of high-dose atorvastatin, this agent is likely to remain the cardiologist's drug of choice for patients presenting with ACS. An interesting concept that remains unexplored is the potential for intravenous administration of a statin; intravenous rosuvastatin has demonstrated efficacy in an animal model of stroke [83]. Given the evidence of very early benefit in the ACS statin trials and the evidence of risk reduction in patients undergoing PCI, the question has to be posed whether statins administered parenterally, for example, at the time of primary percutaneous coronary intervention (PPCI) for ST segment elevation myocardial infarction (STEMI), would enhance myocardial salvage by reducing inflammation. This question is likely to remain unexplored. Our view is that the next clinically meaningful advance in this therapeutic area is likely to come from adjuncts that provide more profound LDL-C lowering when combined with high-dose statins [84]; these agents need to be evaluated in randomised clinical trials to evaluate their safety and efficacy when administered early in conjunction with high-dose statins in the setting of ACS.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Affiliation

Rajesh K Aggarwal[†1] MD FRCP (Lond) & Refai Showkathali[2] MBBS MRCP (UK)
[†]Author for correspondence
[1]Consultant Cardiologist,
Basildon University Hospital,
Essex Cardiothoracic Centre,
Basildon, UK
Tel: +44 08451553111, ext 4326;
Fax: +44 01268394334;
E-mail: Rajesh.Aggarwal@btuh.nhs.uk
[2]Speciality Trainee in Cardiology,
Basildon University Hospital,
Essex Cardiothoracic Centre,
Basildon, UK