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Review Article

Is Early Management of Acute Coronary Syndrome with Rosuvastatin Important?

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Abstract

Acute coronary syndrome (ACS) continues to be a leading reason for premature death in both developing and developed nations despite significant advancements in its prevention and therapy. The initial period following an ACS is very critical with chances of risk of recurrent episodes; hence, the stabilization of susceptible coronary plaques is warranted. Statins have been strongly recommended for the prevention and management of cardiac diseases in several clinical guidelines for two decades. They are known to suppress the pathologic processes that lead to ACS episodes. Rosuvastatin is documented as the most potent statin in lowering lipid profiles and inflammatory markers associated with atherosclerosis. Early initiation of high-dose rosuvastatin therapy has been shown to produce significantly positive results and meet the goals of various clinical guidelines in lowering low-density lipoprotein values. The superiority in the effectiveness as well as the potency of rosuvastatin over atorvastatin in lowering lipid profiles and inflammatory markers and causing a reduction in the atherosclerotic burden has been reported in many studies. Few studies found no difference in the effectiveness of these two drugs. Hence, this paper aims to review the recent scientific evidence and guidelines to ascertain the role of rosuvastatin in the management of ACS.

Keywords: Acute coronary syndrome, Atorvastatin, Cardiovascular disease, Rosuvastatin, Secondary prevention, Statins

INTRODUCTION

Coronary artery disease (CAD) is perhaps the most significant reason for early morbidity and mortality in both industrialized and developing nations.[1] Acute coronary syndrome (ACS) is among the most frequent presentations of CAD.[2] ACS is triggered by the acute obstruction of the coronary vessels, and it includes conditions such as unstable angina, ST-elevation myocardial infarction (STEMI), and non-STEMI (NSTEMI).[3] Multiple ACS registries in India report the prevalence of STEMI as 37–72.4%, NSTEMI as 27.8–54.5%, and overall mortality as varying between 2.04% and 10.2%.[1] The period immediately after an episode of ACS is critical with a considerable risk of frequent episodes and mortality from vulnerable plaque occlusion. Hence, measures to treat susceptible plaques are crucial. Numerous treatment strategies, including antithrombotic drugs, beta-blockers, and angiotensin-converting enzyme inhibitors, were previously employed to stop episodes after ACS; however, the likelihood of catastrophic events remained high.[4] The advent of statins as a frontline treatment in the management of ACS has significantly reduced cardiovascular risks and events.[5-8] These drugs are known to suppress inflammation, endothelial dysfunction, and thrombus development, all of which are involved in the mechanism of ACS.[8]

Statins are extensively recognized for the prevention of cardiac diseases in several clinical guidelines, such as the American College of Cardiology (ACC)/American Heart Association (AHA) task force and European society of cardiology (ESC)/European atherosclerosis society (EAS) and have already been incorporated in the World Health Organization (WHO) guidelines for cardiovascular disease prevention from 2007.[6,9] In addition, WHO's target by 2025 is to achieve 50% coverage of statin therapy among eligible people who already have cardiovascular ailments or are at risk of acquiring them.[9] The 2019 guidelines from the ESC and EAS state that each patient's response to statin therapy differs and hence recommend raising the statin dose before starting any further low-density lipoprotein (LDL)-lowering therapies.[10]

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Literature has described the three generations of statins depending on their increased potency in decreasing LDL cholesterol (LDL-C) values. The third-generation, such as rosuvastatin and pitavastatin, is known as superstatins because of their high potency and efficacy.[7] The high potency of rosuvastatin is attributed to its fluorinated phenyl group and methane sulfonamide along with the side chain of dihydroxyheptenoic acid structure. The unique chemical composition and thermodynamically lowest free energy (ΔG) values of this molecule are responsible for its high binding affinity with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzymes when compared to other statins.[7,11] In addition, rosuvastatin is not extensively metabolized, only 10% of it is metabolized by the interactions with cytochrome-P450-2C9 enzyme, cytochrome-P450-2C19 enzyme, organic anion transporting polypeptide 1B1, and breast cancer resistance protein.[12,13] The hydrophilic nature of rosuvastatin prevents drug interactions and inhibits biotransformation into water-soluble metabolites for elimination. Compared to other statins, rosuvastatin interacts less with other drugs as it is mainly metabolized by CYP2C9.[7]

A systematic review of 42 trials concluded that the lipid-lowering capacity of the commonly used atorvastatin ranged from 37 to 51% and was 3 times less effective than the newer agent rosuvastatin.[14] Rosuvastatin is concluded to be the most potent statin in lowering blood levels of LDL-C, apolipoprotein B (Apo-B), and total cholesterol and increasing high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 (Apo-A1).[15,16] It is also effective in lowering coronary atherosclerotic plaques.[10,17,18]

In addition, rosuvastatin is available in a range of doses (5–40 mg), providing health-care professionals the ability to adjust treatment doses to maximize the therapeutic benefit while simultaneously minimizing adverse effects.[10] Hence, this paper aims at reviewing the recent scientific evidence and guidelines to ascertain the role of rosuvastatin in the management of ACS.

POTENTIAL MECHANISM OF ACTION OF ROSUVASTATIN IN ACS MANAGEMENT

Statins are a group of amphiphilic structures and are frequently preferred drugs for the effective management of dyslipidemia.[11] They inhibit the production of endogenous cholesterol, especially in hepatic cells, which lowers cellular cholesterol levels and boosts the activity of LDL receptors on hepatocytes. Enhanced LDL receptor concentration leads to the catabolism of atherogenic lipoproteins and inhibits hepatic very LDL production. In addition, statins elevate HDL and reduce the imbalance between atherogenic and antiatherogenic lipoproteins, which improves the nature and integrity of atherosclerotic lesions [Figure 1].[8,11,19]

Statins offer multiple pleiotropic benefits, such as increased anti-inflammatory, antioxidant, and antiplatelet effects, coronary plaque stabilization, enhancement of endothelial

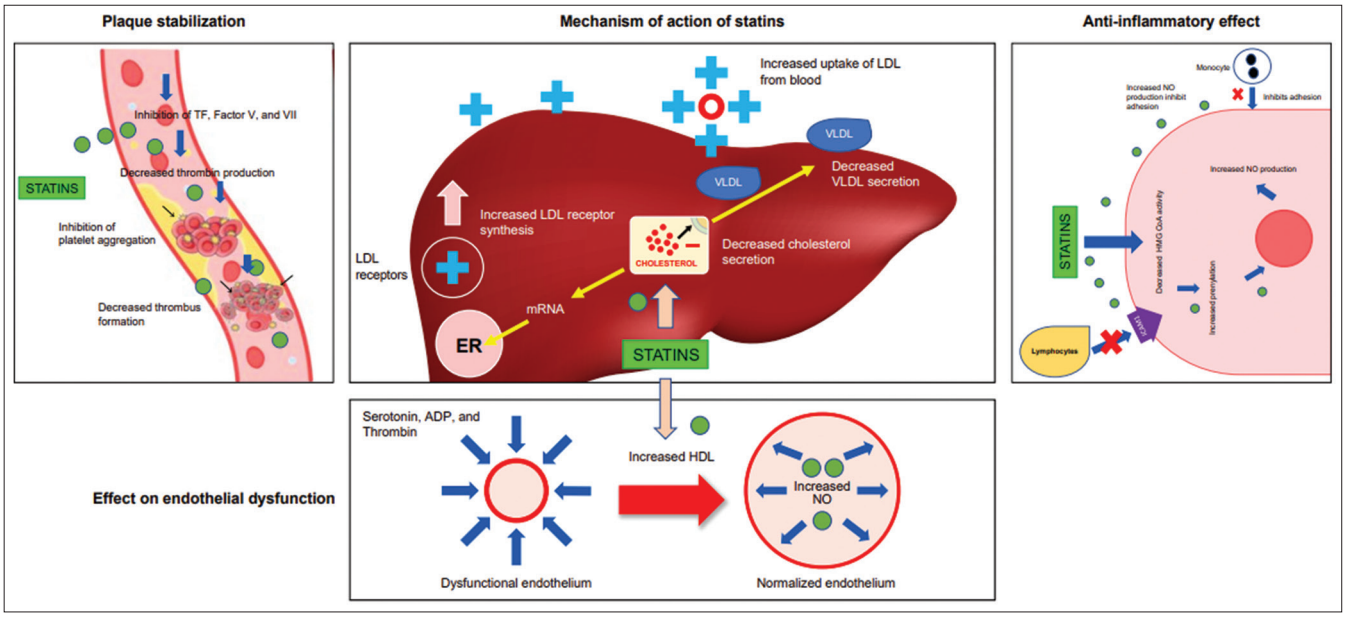

Figure 1: Mechanism of action of statins in preventing ACS episodes. ACS: Acute coronary syndrome; ADP: Adenosine diphosphate; ER: Endoplasmic reticulum; HDL: High-density lipoprotein; HMG CoA: 3-Hydroxy-3-methylglutaryl coenzyme A; ICAM1: Intercellular adhesion molecule 1; LDL: Low-density lipoprotein: mRNA: Messenger ribonucleic acid; NO: Nitric oxide; TF: Tissue factor; VLDL: Very low-density lipoprotein

function, and an increase in adiponectin, which suppresses the cascade of events in ACS.[6,8] Therefore, these pleiotropic effects strongly support the idea of utilizing statins to treat ACS.

Anti-inflammatory Effect

Inflammation plays a vital role in atherosclerosis progression and the formation of coronary lesions. Higher concentrations of several inflammatory markers, such as serum amyloid A, C-reactive protein (CRP), interleukin-6 (IL-6), heat-shock protein 65, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion protein 1, are associated with the severity and prognosis of atherosclerosis. It is well known that statins lower CRP levels. In addition, statins reduce the production of monocyte chemoattractant protein-1, tumor necrosis factor-alpha, IL-1, IL-8, and matrix metalloproteinase. The mechanism involved in the anti-inflammatory effect is mentioned below:

1. Inhibiting lymphocyte adhesion: By directly interacting with ICAM-1, statins reduce T-cell activation and decreases lymphocyte adherence to endothelial cells
2. Altering the Rho–Rho-kinase pathway: Statins block the mevalonate pathway by inhibiting HMG-CoA reductase. This reduces the intracellular pool of isoprenoids, which, in turn, inhibits the prenylation activity. Decreased prenylation further inhibits the stimulation of nuclear factor-kB and boosts the production of nitric oxide synthase (NOS)
3. Lowering serum LDL levels: Oxidized LDL inhibits NO production and suppresses endothelial NOS activity. Statins lower plasma LDL levels, which, in turn, reduce the production of oxidized LDL. Thus, statin therapy enhances NO bioavailability and lowers monocyte adherence to epithelial cells by lowering LDL substrate [Figure 1].[8,19]

Plaque Stabilization

Treatment with statins decreases the expression of tissue factors on macrophages, which prevents the triggering of the coagulation system. In addition, statins prevent the production of thrombin by suppressing the activation of factors V, Va, and factor VII. Finally, statins also inhibit the activation of factor XIII and inhibit the formation of clots. Furthermore, statins reduce platelet aggregation, which prevents thrombus formation [Figure 1].[8,19]

Effect on Endothelial Dysfunction

Endothelial dysfunction occurs when an imbalance arises between the compensatory mechanisms that cause vasoconstriction and vasodilation. The dysfunctional endothelial cells become vasoconstrictive following acute cardiovascular events in response to various stimuli, including thrombin, serotonin, adenosine diphosphate, reduced intracoronary blood pressure, and other factors. Statins increase NO production, which protects against CAD through its vasodilating effects, alteration in the inflammatory reaction, and activation of leukocytes and platelets. In addition, statin-mediated decrease in atherogenic lipoproteins and increase in HDL improve endothelial function.[8,19] Figure 1 represents the various mechanisms by which statins prevent ACS episodes, including plaque stabilization, anti-inflammatory effect, and the reduction in endothelial dysfunction.

EVIDENCE FOR EARLY INITIATION OF ROSUVASTATIN THERAPY IN ACS

The management of ACS is significantly influenced by the degree of occlusion and the timing of the onset of symptoms. The acute phase is managed by antithrombotic drugs, percutaneous coronary intervention (PCI), and heart bypass surgery. The secondary level of prevention involves changing one's lifestyle and behavior (smoking cessation, exercising, etc.) and the use of medications. Adequate compliance with the suggested treatment regimen usually ensures an enhancement in the quality of life and a reduction in subsequent ischemic episodes and death in ACS cases.[20]

The AHA/ACC and the ESC advise that, before discharge, all patients should be given medications as a secondary level of prevention after an ACS.[20] Furthermore, ESC/EAS guidelines suggest that the intake of statin should begin 1–4 days after an ACS-related hospitalization. Japanese guidelines also recommend management using early statin therapy in all patients with STEMI therapy. The ESC/EAS guidelines' "treat-to-target" strategy of a 50% decrease from the baseline values of LDL-C in patients with ACS, validates the use of strong statins as early-phase therapy. Thus, early and intensive lipid-lowering therapy with statins is currently recommended worldwide.[6]

Based on LDL-C being reduced, the intensity of statin therapy is categorized into three groups: high intensity aims to reduce by 50%, moderate intensity by 30–49%, and low intensity by <30% LDL-C. The dosage of 20–40 mg/day for rosuvastatin and 40–80 mg for atorvastatin is classified as high intensity, whereas the dosage of 5–10 mg and 10–20 mg is classified as moderate intensity for rosuvastatin and atorvastatin, respectively.[21]

ROLE OF HIGH-INTENSITY ROSUVASTATIN IN ACS

The implications of prescribing high-intensity rosuvastatin treatment during the initial phase of ACS had several

benefits. A study by Luo *et al.* (2022) shows that high-dose rosuvastatin therapy has a stronger therapeutic impact than regular-dose rosuvastatin for enhancing lipid metabolic activity, lowering inflammatory process, and managing ventricular remodeling and fibrosis of myocardium.[22] A meta-analysis has reported that preloading with high-dose rosuvastatin significantly improves myocardial perfusion and reduces both cardiac events and myocardial injury in PCI patients.[23]

Studies using high-dose rosuvastatin during the initial phase of ACS treatment are summarized in Table 1. Most of the studies showed a significant decrease in primary outcome values from baseline values. Reduction in LDL-C was reported by yellow, lunar, asteroid, Stellar, Centaurus, and orion trials. An increase in HDL was reported by LUNAR and ASTEROID trials. The CENTAURUS trial indicated a reduction in the Apo-B/Apo-A1.

ROLE OF MODERATE-INTENSITY ROSUVASTATIN IN ACS

Very few studies have evaluated the efficiency of moderate-dose rosuvastatin during the early phase of ACS. The multicentric SPACE ROCKET trial evaluated the effectiveness of 10 mg of rosuvastatin over 40 mg of simvastatin for the secondary prevention of ACS episodes. Rosuvastatin decreased LDL-C and TC by 78 mg/dL and 150 mg/dL, respectively. A total of 79.9% of patients met the lipid target goals of ESC-2003.[31] In the PULSAR trial, 10 mg of rosuvastatin was evaluated on 996 individuals who

Table 1: Evidence for early initiation of high-dose rosuvastatin therapy in ACS

Author, Year	Study population; sample size	Drug	Endpoints	Duration	Outcome
Kini *et al*.; 2013 (Yellow)[24]	CAD; 87	RSV40 versus standard care	Change in LCBI at the 4-mm maximal segment in the lesion	7 weeks	LDL-C and TC decreased. CRP levels remained unchanged. There was a reduction in LCBI 4 mm max. Short-term intensive therapy may reduce lipid content in obstructive lesions.
Pitt *et al*.; 2012 (LUNAR)[25]	ACS; 825	RSV20/RSV40 versus ATV80	LDL-C, HDL Apo-A1, Apo-B/Apo-A1	6–12 weeks	RSV40 was effective in improving Apo-A1 and several lipid ratios, including LDL-C/HDL-C, non-HDL-C/HDL-C, TC/HDL-C, and Apo-B/Apo-A1.
Nicholls *et al*.; 2011[26]	CAD; 1039	RSV40 versus ATV80	PAV, TAV	104 weeks	Decrease in LDL-C and increase in HDL-C values. The decrease in PAV was 1.22%. The reduction in normalized TAV was−6.99 mm^3. The percentage of patients who showed regression for PAV was 68.5% with RSV40.
Lablanche *et al*.; 2010 (CENTAURUS)[27]	ACS; 753	RSV20 versus ATV80	Apo-B/Apo-A1 ratio	3 months	RSV20 was effective in decreasing the Apo-B/Apo-A1 ratio, and LDL-C decreased by~50%.
Chhatriwalla *et al*.; 2006 (ASTEROID)[28]	CAD; 349	RSV40	PAV, TAV	24 months	Mean LDL-C decreased by 53.2% and mean HDL-C increased by 14.7%. A significant reduction in PAV (−0.79%) and TAV (−12.5 mm3) was observed.
Jones *et al*.; 2003 (Stellar)[16]	Hypercholesterolemia; 2431	RSV10, RSV20, RSV40	LDL-C, HDL, triglycerides, TC	6 weeks	LDL-C: The percentage decrease for RSV20 and RSV40 was 52.4% and 55%, respectively. HDL: Percentage increase change for RSV20 and RSV40 was 9.5% and 9.6%, respectively. Triglycerides: The percentage decrease for RSV20 and RSV40 was 23.7% and 26.1%, respectively. TC: The percentage decrease for RSV20 and RSV40 was 37.6% and 40.2%, respectively.
Underhill *et al*.; 2008 (ORION)[29]	Moderately hypercholesterolemic patients; 43	RSV5 or RSV40/RSV80	Carotid plaque volume and composition	24 months	RSV40/RSV80 reduced LDL by 59.9%, and no significant changes in carotid plaque volume were observed. There was a 41.4% reduction in the lipid-rich necrotic core.

ACS: Acute coronary syndrome, Apo-A1: Apolipoprotein-A1, Apo-B: Apolipoprotein-B, ATV: Atorvastatin, CAD: Coronary artery disease, CRP: C-reactive protein, HDL-C: High-density lipoprotein cholesterol, LCBI: Lipid-core burden index, LDL-C: Low-density lipoprotein cholesterol, PAV: Percent atheroma volume, PCI: Percutaneous coronary intervention, RSV: Rosuvastatin, TAV, Total atheroma volume, TC: Total cholesterol

had atherosclerosis or CAD or were at risk of developing CAD. Rosuvastatin slashed LDL-C by 44.6% and enhanced HDL-C by 6.4%. Approximately 68% of patients met the ESC-2003 (<2.5 mmol/L [100 mg/dL]) and the National Cholesterol Education Program Adult Treatment Panel III LDL-C (<2.6 mmol/L) goal.[31] Another multicentric COSMOS trial was conducted in Japan among 214 patients with stable CAD using 2.5 mg/day rosuvastatin as the initial treatment. After 76 weeks, LDL-C had reduced by 38% and HDL-C had risen by 19.8%. Sixty percent of patients experienced plaque regression.[32]

COMPARISON WITH ATORVASTATIN

A plethora of literature including meta-analysis and RCTs has concluded the superiority of rosuvastatin in lowering serum levels of lipid and inflammatory markers over atorvastatin. However, very few studies failed to report differences between them for primary outcomes.

Meta-analysis among Caucasians has shown that the efficacies of all doses of rosuvastatin are 3–3.5 times more potent than those of equivalent therapy of atorvastatin. With 5 mg of rosuvastatin, LDL-C and non-HDL-C were reduced by 39% and 35%, respectively. It took 15 mg of atorvastatin for LDL-C and 14 mg for non-HDL-C to lower the same amount. Rosuvastatin 10 mg lowered LDL-C by 44% and non-HDL-C by 40%, whereas 29 mg and 27 mg of atorvastatin were required to attain comparable reduction. LDL-C was lowered by 50% and non-HDL-C by 45% with rosuvastatin 20 mg, whereas 70 mg and 62 mg of atorvastatin were required to attain a similar reduction. A maximum dose of 80 mg of atorvastatin did not result in a comparable reduction of LDL-C and non-HDL-C with a 40 mg dose of rosuvastatin.[33]

Another meta-analysis among Southeast Asian populations by Zhang *et al*. included 16 RCTs with 5930 participants. When atorvastatin and rosuvastatin were compared, patients on rosuvastatin had significantly lower LDL-C (weighted mean difference [MD] = 7.15 mg/dL; 95% confidence interval: 10.71−3.60 mg/dL; $P = 0.0001$). Age, gender, LDL-C, and follow-up did not affect the advantages of rosuvastatin in meta-regression analysis.[34]

Rosuvastatin was demonstrated to be more potent than atorvastatin for lowering the volume of coronary atherosclerotic plaque. Atheroma volume percent decrease (MD: 0.36 [0.65–0.05]; $P = 0.02$) and atheroma total reduction (MD: 1.63 [2.86–0.41]; $P = 0.0009$) were higher in the rosuvastatin group. Furthermore, LDL-C reduced while HDL-C increased.[18] According to another meta-analysis of five RCTs, rosuvastatin offered enhanced benefits over atorvastatin in the regression of atherosclerotic lesions.[17]

A comparison of rosuvastatin and atorvastatin is presented in Table 2. The studies are combined based on primary outcomes.

Table 3 compares the efficacy of rosuvastatin and atorvastatin for various parameters. The tick (✔) shows rosuvastatin was more potent than atorvastatin, whereas the cross (X) denotes no significant difference between the drugs for that parameter.

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 INHIBITORS (PCSK9I)—CONSIDERATIONS FOR USE IN ACS

Although statins are used as frontline therapy drugs in ACS patients, many individuals also require additional therapy to meet their target goals in lowering LDL-C values.[46] With the introduction of PCSK9i, the concept of lipoprotein metabolism has been drastically altered. The enzyme PCSK9 hinders the elimination of LDL-C by accelerating the degradation of LDL receptors.[47] Patients with familial hyperlipidemia and atherosclerotic cardiovascular disease (ASCVD) and those who are unable to tolerate high-intensity statins because of adverse effects may require other drugs to reduce serum LDL-C levels such as ezetimibe and PCSK9i. The therapeutic advantages of adding PCSK9i to statin therapy have been shown in the FOURIER and ODYSSEY OUTCOMES investigations. It is significantly more expensive than other lipid-reducing medications while being the most effective in lowering LDL-C.[46,48]

To decrease the LDL-C levels below 70 mg/dL (1.8 mmol/L), the ACC/AHA guidelines advise starting with a rigorous drug regimen. The addition of ezetimibe and anti-PCSK9 antibodies is recommended by ESC/EAS if the ACS patients do not achieve a 50% reduction in LDL-C and LDL-C of >1.4 mmol/L (>55 mg/dL).[49] Overall, the recommendations from the 2018 AHA/ACC and 2019 ESC/EAS guidelines restrict the use of PCSK9i to very high-risk ASCVD cases. According to the Japan atherosclerosis society (JAS) statement from 2018, PCSK9i is exclusively advised for people with CAD.[46] The 2020 Taiwan National Health Insurance regulation, 2018 AHA/ACC guidelines, and 2018 JAS recommend making ezetimibe necessary before adding PCSK9i, whereas the 2019 ESC/EAS guidelines and 2017 National Lipid Association advocate the addition of ezetimibe optional by clinical judgment.[46] Although most patients on PCSK9i achieve the anticipated lowering of 50–60% LDL-C levels from the baseline, there are sporadic reports of patients who have a lesser LDL-C-lowering response.[49]

Table 2: Summary of studies comparing rosuvastatin and atorvastatin

Author; Year	Study population; sample size	Drug	Endpoints	Follow-up	Result
MACE					
Rahhal *et al*.; 2022[35]	ACS; 1253	RSV20 or RSV40 versus ATV40 or ATV80	CVD-associated death, nonfatal ACS, and nonfatal stroke at 1 and 12 months	12 months	No significant difference at 1 and 12 months.
Schuetz *et al*.; 2012[36]		RSV20 versus ATV40 RSV40 versus ATV80	MACE (first occurrence of fatal or nonfatal MI, fatal or nonfatal stroke, or cardiovascular death)	5 years and 20 years	The incidence of MACE was lower in rosuvastatin 20 mg and 40 mg at 5 and 20 years.
hs-CRP					
Tran *et al*.; 2021[37]	ACS; 96	RSV20 versus ATV40	LDL-C and hs-CRP levels	4 days	No difference between the groups for LDL-C and hs-CRP.
Umrani *et al*.; 2020[38]	ACS; 128	RSV40 versus ATV20	hs-CRP and ESR	4 weeks	Rosuvastatin was superior.
Kumar *et al*.; 2019[39]	ACS; 207	RSV40 versus ATV20	hs-CRP and ESR	4 weeks	RSV was superior in reducing hs-CRP (51% versus 35%) and ESR levels (16% versus 14%).
Mostafa *et al*.; 2018[40]	ACS; 100	RSV40 versus ATV80	ESR, hs-CRP, and TLC after 4 weeks; lipid profile after 3 months	3 months	No significant difference for ESR, hs-CRP, or TLC. RSV was more potent for reducing LDL-C and increasing levels of liver enzymes, alanine, and aspartate aminotransferases.
Khurana *et al*.; 2015[41]	ACS; 100	RSV20 versus ATV40	CRP, lipid profiles, ESR	4 weeks	RSV was more effective in reducing CRP (44% versus 35%).
LDL-C					
Altunkeser *et al*.; 2019[42]	ACS; 106	RSV40 versus ATV80	LDL-C, oxidized-LDL, and triglyceride levels	4 weeks	No significant difference was observed.
Aydin *et al*.; 2015[43]	STEMI; 121	RSV20 versus ATV80	LDL-C, oxidized-LDL, hs-CRP, TNF-1 and 2, IL-6, HDL-C level	4 weeks	No significant difference for LDL-C, oxidized-LDL, hs-CRP, TNF-1 and 2, and IL-6. HDL-C increased with RSV20.
Pitt *et al*.; 2012 (LUNAR)[25]	ACS; 825	RSV20/RSV40 versus ATV80	LDL-C, HDL-C	6–12 weeks	RSV20≈ATV80; RSV40>ATV80 for LDL-C. HDL-C was significantly greater with RSV20/RSV40.
Clearfield *et al*.; 2006 (PULSAR)[31]	Hypercholesterolemia, CHD, atherosclerosis, or CHD risk; 996	RSV10 versus ATV20	LDL-C	6 weeks	RSV10 reduced LDL-C significantly more than ATV20.
Jones *et al*.; 2003 (STELLAR)[16]	Hypercholesterolemia; 2431	RSV10, RSV20, RSV40 versus ATV10, ATV20, ATV40, ATV80	LDL-C, HDL, triglycerides, TC	6 weeks	RSV was more efficient than ATV for non-HDL-C.
Apo-B/Apo-A1 ratio					
Lablanche *et al*.; 2010 (CENTAURUS)[27]	ACS; 753	RSV20 versus ATV80	Apo-B/Apo-A1 ratio	3 months	RSV20 was superior at 1 month, whereas no difference at 3 months.
NLR, PLR, and MHR					
Tuncez *et al*.; 2019[44]	STEMI and NSTEMI; 128	RSV40 versus ATV80	NLR, PLR, MHR	1 month	No significant differences between the groups for NLR, PLR, and MHR. Both the statins did not affect PLR.
Oxidative parameters					
Kilit *et al*.; 2017[45]	AMI; 55	RSV40 versus ATV80	Serum paraoxonase, serum arylesterase, TAS, and OSI	4 weeks	No significant difference in oxidative parameters. HDL-C was raised by RSV40 more than ATV80.

(Contd...)

Table 2: *(Continued)*

Author; Year	Study population; sample size	Drug	Endpoints	Follow-up	Result
Atheroma burden Nicholls *et al*.; 2011[26]	CAD; 1039	RSV40 versus ATV80	PAV, TAV	104 weeks	Both PAV and TAV decreased significantly higher with RSV40.

ACS: Acute coronary syndrome, AMI: Acute myocardial infarction, Apo-A1: Apolipoprotein-A1, Apo-B: Apolipoprotein-B, ATV: Atorvastatin, CAD: Coronary artery disease, CHD: Coronary heart disease, CVD: Cardiovascular disease, ESR: Erythrocyte sedimentation rate, HDL-C: High-density lipoprotein cholesterol, hs-CRP: High-sensitivity C-reactive protein, IL: Interleukin, LCBI: Lipid-core burden index, LDL-C: Low-density lipoprotein cholesterol, MACE: Major adverse cardiac events, MI: Myocardial infarction, MLR: Monocyte-to-high-density lipoprotein cholesterol ratio, NLR: Neutrophil-to-lymphocyte ratio, NSTEMI: Non–ST-segment elevation myocardial infarction, OSI: Oxidative stress index, PAV: Percent atheroma volume, PCI: Percutaneous coronary intervention, PLR: Platelet-to-lymphocyte ratio, RSV: Rosuvastatin, STEMI: ST-elevation myocardial infarction, TAV: Total atheroma volume, TAS: Total antioxidant status, TC: Total cholesterol, TLC: Total leukocyte count, TNF: Tumor necrosis factor

Table 3: Comparison of rosuvastatin and atorvastatin

Author; Year	Drug	LDL-C	HDL-C	CRP	ESR	Atheroma burden	Apo-B/Apo-A1 ratio	MACE	Others
Rahhal *et al*.; 2022[35]	RSV20 or RSV40 versus ATV40 or ATV80							X	
Tran *et al*.; 2021[37]	RSV20 versus ATV40	X		X					
Umrani *et al*.; 2020[38]	RSV40 versus ATV20			✔	✔				
Kumar *et al*.; 2019[40]	RSV40 versus ATV20			✔	✔				
Altunkeser *et al*.; 2019[42]	RSV40 versus ATV80	X (LDL-C, oxidized-LDL)							X (NLR, PLR, MHR)
Tuncez *et al*.; 2019[44]	RSV40 versus ATV80								X (NLR, PLR, MHR)
Mostafa *et al*.; 2018[40]	RSV40 versus ATV80	✔		X	X				X (TLC)
Kilit C *et al*.; 2017[45]	RSV40 versus ATV80		✔						X (Serum paraoxonase, serum arylesterase, TAS, and OSI)
Aydin *et al*.; 2015[43]	RSV10 or ATV80	X (LDL-C, oxidized-LDL)	✔	X					X (TNF-1 and TNF-2 and IL-6)
Khurana *et al*.; 2015[41]	RSV40 versus ATV80			✔					
Pitt *et al*.; 2012 (LUNAR)[25]	RSV20 or RSV40 versus ATV80	✔ (RSV40)	✔						
Schuetz *et al*.; 2012[36]	RSV20 versus ATV40 and RSV40 versus ATV80							✔	
Nicholls *et al*.; 2011[26]	RSV40 versus ATV80					✔ (PAV, TAV)			
Lablanche *et al*.; 2010 (CENTAURUS)[27]	RSV20 or RSV40 versus ATV80						✔ (at 1 month) X (at 3 months)		
Clearfield *et al*.; 2006 (PULSAR)[31]	RSV10 versus ATV20	✔							
Jones *et al*.; 2003 (STELLAR)[16]	RSV10, RSV20, RSV40, RSV80 versus ATV10, ATV20, ATV40, ATV80	✔							

Apo-A1: Apolipoprotein-A1, Apo-B: Apolipoprotein-B, ATV: Atorvastatin, hs-CRP: High-sensitivity C-reactive protein, ESR: Erythrocyte sedimentation rate, HDL-C: High-density lipoprotein cholesterol, IL: Interleukin, LDL-C: Low-density lipoprotein cholesterol, MACE: Major adverse cardiac events, MLR: Monocyte-to-high-density lipoprotein cholesterol ratio, NLR: Neutrophil-to-lymphocyte ratio, OSI: Oxidative stress index, PAV: Percent atheroma volume, PLR: Platelet-to-lymphocyte ratio, RSV: Rosuvastatin, TAV: Total atheroma volume, TAS: Total antioxidant status, TC: Total cholesterol, TLC: Total leukocyte count, TNF: Tumor necrosis factor

In addition to the controversy surrounding the use of PCSK9i in the literature, the availability of such novel therapy is an additional concern. The expense involved in PCSK9i therapy prevents its broad use; therefore, this therapy is usually restricted to patients with a substantial risk of ASCVD complications. Numerous studies conducted in Western countries on the economic evaluation of PCSK9i therapy have generally concluded that they are not economically viable at the current cost. Hence, appropriate and judicious use should be the guiding factor in the current scenario.[50]

GUIDELINE RECOMMENDATIONS

There are multiple guidelines for the management of dyslipidemia in the treatment of ACS. Most of these guidelines advocate intense lipid-reduction therapy for

Table 4: Clinical guidelines for the management of ACS

Guidelines	Threshold versus goals in ACS patients	Treatment strategy
ESC guidelines	• LDL goals in ACS patients are both a reduction of≥50% and<55 mg/dL. • LDL goal in recurrent ASCVD events within 2 years is<40 mg/dL.	• Healthy lifestyle. • High-intensity maximal statin. • If LDL-C≥55 mg/dL within 4–6 weeks, add ezetimibe. • If LDL-C≥55 mg/dL within 4–6 weeks, add PCSK9i. • If LDL-C≥40 mg/dL within 4–6 weeks and recurrent ASCVD event within 2 years, may add PCSK9i.

ACC: American college of cardiology, ACS: Acute coronary syndrome, AHA: American Heart Association, ASCVD: atherosclerotic cardiovascular disease, ESC: European Society of Cardiology, LDL-C: Low-density lipoprotein cholesterol, PCSK9i: Proprotein convertase subtilisin kexin 9 inhibitors

higher risk. However, the parameters for risk estimation vary among guidelines. Over the years, the ESC guidelines have developed very strict parameters and recommend the use of statin to achieve lipid-related goals. The AHA/ACC guidelines do not recommend combination treatments very frequently and do so only for individual cases.[51] All guidelines support the use of non-fasting lipid profiles for screening and propose LDL-C level as the gold standard for the assessment in the diagnosis and management of cases.[52] Table 4 presents a comparison of the American and European secondary preventive guidelines for ACS.[52]

ADVERSE EFFECTS OF ROSUVASTATIN

Rosuvastatin has a safety profile equivalent to other approved statins when administered in a range of 10–40 mg doses. Rosuvastatin is sharing the adverse effects of other statins and is dose dependent. Various side effects of statins include musculoskeletal complaints (myalgia, muscle stiffness, and weakness), elevated creatine kinase, myopathy, rhabdomyolysis, liver dysfunction (elevation of alanine transaminase and aspartate transaminase), renal insufficiency, gastrointestinal effects (diarrhea, constipation, nausea, abdominal pain, and dyspepsia), central nervous system effects (headache, dizziness, and paresthesias), interstitial lung disease, and cardiovascular conditions (myocardial infarction and death).[5,53,54] However, the risks of severe myopathy, rhabdomyolysis, and renal failure are lower for rosuvastatin than those of other statins.[53] On the contrary, the JUPITER study demonstrates that rosuvastatin is linked to a slight increase in the incidence of diabetes mellitus in elderly individuals with other comorbidities.[53,55]

CLINICAL TIPS

Statins are the preferred frontline drug of choice in decreasing lipid levels and preventing recurrent cardiac episodes. The "earlier the intervention, the greater the benefit" strategy can be applied when a patient first presents for evaluation for ACS.[56] As the superior efficacy of rosuvastatin in the management of ACS has been convincingly demonstrated, it can be preferred over other statins wherever indicated. Physicians should evaluate each patient's comorbidities, lipid profiles, and statin-related adverse effects to determine the optimal statin type and dose.[57,58]

A higher dose of rosuvastatin should be decided based on increasing cardiovascular risks, and the risk should be determined using evidence-based tools from standard guidelines. Patients should be well-informed and engaged in discussion before initiating statin therapy and lifestyle changes. In addition, patients should be routinely monitored for compliance with lifestyle changes and appropriate intensity of statin therapy. Combination therapy should be considered if a statin alone does not sufficiently lower cholesterol levels.[58]

CONCLUSION

Statins are the preferred agents for the effective management of dyslipidemia. In addition, the pleiotropic effects greatly promote the application of statins in treating ACS. This review paper demonstrates that rosuvastatin showed an improvement in lipid profile and inflammatory markers. Rosuvastatin appeared to be superior to atorvastatin in lowering LDL-C and Apo-B and increasing Apo-A1. Early initiation of high-intensity rosuvastatin is more beneficial in ACS as it not only promotes treatment adherence but also reduces the risk of new events. Non-statin treatments, such as ezetimibe and PCSK9i, are effective in lowering LDL-C along with statins. Although rosuvastatin is linked to various adverse effects, it is safe when used at appropriate doses and patients are monitored regularly. Collaborative decision-making should be used to commence statin treatment.

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AUTHORS' CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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