INDIAN SOCIETY OF HYPERTENSION

Hypertension Journal

Review Article

High Intensity Statins in Acute Coronary Syndrome Part II: A comparison of Atorvastatin and Rosuvastatin for use in ACS, Clinical trials in India and Place for statins in current guidelines

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Abstract

This manuscript provides an in-depth analysis of the two most prescribed high-intensity statins, evaluating their respective impacts on lipid profiles, inflammatory markers, and clinical outcomes in patients with ACS. Furthermore, this essay explores the landscape of clinical trials conducted in India concerning statin usage in ACS, and critically assesses the placement of statins within contemporary guidelines, underscoring their pivotal role in the management of ACS.

Keywords: Acute Coronary Syndrome, Statins.

DOI: 10.61081/htnj/23v9i204

INTRODUCTION

The role of high-intensity statins in the management of Acute Coronary Syndrome (ACS) has been a focal point of cardiovascular research, with a particular emphasis on comparing the efficacy and safety of Atorvastatin (ATV) and Rosuvastatin (RSV) in mitigating cardiovascular risk. This manuscript provides an in-depth analysis of the two most prescribed high-intensity statins, evaluating their respective impacts on lipid profiles, inflammatory markers, and clinical outcomes in patients with ACS. Furthermore, this essay explores the landscape of clinical trials conducted in India concerning statin usage in ACS, and critically assesses the placement of statins within contemporary guidelines, underscoring their pivotal role in the management of ACS. Table 1 discusses the important studies that have been done on Rosuvastatin use in ACS.

Atorvastatin Vs Rosuvastatin in ACS

A meta-analysis published in 2014[10] has studied 28 RCT's on Atorvastatin vs Rosuvastatin on Apolipoprotein profiles of patients.[5,11-37] The analysis found that rosuvastatin can achieve a greater reduction in LDL without an increased risk of side effects when compared to the same or even double the dose of atorvastatin. Particularly at a 1/4 dose ratio, both drugs show comparable lipid-lowering effects and safety outcomes. Additionally, rosuvastatin holds a more favorable benefit-risk profile than its counterpart. In terms of HDL cholesterol elevation, rosuvastatin and simvastatin have been observed to be superior to atorvastatin. Moreover, the HDL-raising capability of rosuvastatin is found to be dose-dependent, whereas it's inversely related to atorvastatin. On the adverse events front, there isn't a significant difference between the two statins in terms of side effects like myalgia, creatine kinase elevation, or cancer. However, higher doses of both drugs are linked to more discontinuations, with atorvastatin specifically showing a higher likelihood of liver enzyme elevation at increased doses. The importance of Apolipoprotein B (ApoB) as a cardiovascular risk predictor has been highlighted, with it outperforming both LDL and non-HDL cholesterol as a risk marker. The study also pointed to rosuvastatin's consistent performance in ApoB reduction across various doses, with certain exceptions at the higher spectrum. Interestingly, while rosuvastatin's influence on ApoA-I, another lipoprotein, isn't dose-dependent, atorvastatin's impact decreases as its dose increases. It's worth noting that there are certain limitations to these findings, including a potential bias towards rosuvastatin due to its later market entry. The research methodology primarily employed a fixed-effects estimate, which assumes consistent effects across studies, but the presence of unexplained variability between studies suggests that a random-effects model might be more appropriate. In summary, both statins effectively modify lipid profiles, but rosuvastatin often presents a more favorable outcome in many respects.

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Study done on Rosuvastatin in ACS	Conclusion
LUNAR[1]	In conclusion, results from the LUNAR study show that RSV40 more effectively decreased lowering low-density lipoprotein (LDL) cholesterol, increased HDL cholesterol, and improved other blood lipid parameters than ATV80 in patients with ACS.
SPACE ROCKET[2] & GEOSTAT-1[3]	Rosuvastatin 10 mg lowered mean cholesterol more effectively than simvastatin and achieved better results for the latest, more stringent, ESC target. The LDL cholesterol target was achieved more frequently for 1 in 3 patients with CYP3A5 and/or BCRP variant genotypes when prescribed rosuvastatin 10 mg, compared with simvastatin 40 mg.
CENTAURUS[4,5]	In conclusion, in patients with recent ACS, there was no significant difference between rosuvastatin 20 mg and atorvastatin 80 mg in terms of reduction of the apoB/apoA-1 ratio at 3 months. Thus, the primary endpoint was not met. However, rosuvastatin 20 mg significantly decreased the apoB/apoA-1 ratio at 1-month compared with atorvastatin 80 mg.
ROSUVEES-2[6]	It can be concluded from the results of this study that 40 mg dose of rosuvastatin, initiated early and continued for 12 weeks, was effective in terms of reducing LDL cholesterol and was well tolerated.
KARANCHI RCT's[7,8]	Rosuvastatin led to a 50% decrease in HsCRP/ESR reduction. As compared to Atorvastatin which showed just 35% decrease. In this study, rosuvastatin was significantly superior to atorvastatin in reducing inflammatory markers such as ESR and hsCRP in patients suffering from ACS. Cardiologists should consider using rosuvastatin rather than atorvastatin in the management of patients suffering from ACS with elevated inflammatory biomarkers.
QATARI RCS[9]	This study suggests that the use of high-intensity rosuvastatin, mainly 20 mg, in secondary prevention post-ACS has a comparable effectiveness and safety to high-intensity atorvastatin over a one-year follow-up period, which may provide a clinician with evidence-based reassurance and more flexibility in the selection of a high-intensity statin therapy.

This study had a major drawback in terms of that it did not analyze RCT's that measured the Lipid lowering capability of the two statins in ACS. Thrombus formation on atherosclerotic lesions is essential in ACS initiation. Over the course of the disease, inflammation is constantly present. While initially, only markers of myocardial necrosis like troponins were clinically acknowledged in ACS, modern cardiac biomarkers also encompass markers of vascular damage, hemodynamic instability, and inflammation such as hsCRP. These markers are pivotal for assessing patients' risk and individualized treatment plans.

Statins, post-ACS treatment or for those at cardiovascular risk, can modulate hsCRP levels. Specifically, high-dose statins can expedite the reduction of hsCRP levels post-ACS. Comparing atorvastatin and rosuvastatin, the latter was found more efficacious in mitigating micro-inflammation in ACS patients in RCT's performed in Karanchi.[7,8] Additionally, recurrent ASCVD events also indicate potential relations to reductions in inflammatory markers post-initial cardiovascular incident.

Given the paramount role of statins, especially prevalent ones like atorvastatin and rosuvastatin, in tempering inflammatory markers and, in turn, reducing future cardiovascular events, their comparative analysis becomes essential. The current research's significance is amplified given the scarcity of related data from the Indian Subcontinent.

Several studies have supported rosuvastatin's protective effects on ACS patients, especially those with high baseline hsCRP, while research on atorvastatin presents mixed results. Lipid-lowering therapies, especially HMG-CoA reductase inhibitors, are notably effective in minimizing inflammatory markers in ACS, pointing towards a better prognosis. This underlines the need for more research to comprehend the disease process in Indian Subjects.

Clinical Trials in India on Statin Use in ACS

Detailed insight into the prevalence of lipid abnormalities in the Indian population, as represented by the ICMR-INDIAB study.[38] One of the conditions highlighted is hypercholesterolemia, which signifies elevated cholesterol levels in the blood. In this sample, 13.9% of individuals exhibited this condition. Another lipid abnormality, hypertriglyceridemia, which refers to raised triglyceride levels, was present in 29.5% of the sample. A significant concern is the high prevalence of low HDL (High-Density

Lipoprotein) cholesterol levels, with 72.3% or 1,476 individuals falling into this category. HDL is often termed the "*good cholesterol*," and its deficiency can pose a cardiovascular risk.

Dyslipidemia, which encompasses a variety of conditions including the ones previously mentioned, was diagnosed in a staggering 79% or 1,614 of the individuals. On a brighter note, 21.1% or 431 individuals from the sample showed no lipid abnormalities. Diving deeper into the overlaps presented in the results, it was found that 53 individuals had both hypercholesterolemia and low HDL cholesterol, while 32 had both hypercholesterolemia and hypertriglyceridemia. Moreover, 50 individuals had both hypertriglyceridemia and low HDL cholesterol, and 158 were diagnosed with all three conditions. Meanwhile, specific overlaps between hypercholesterolemia, hypertriglyceridemia, low HDL cholesterol, and dyslipidemia were seen in different segments of the population. This study emphasized the alarming prevalence of lipid abnormalities in the Indian demographic. The extensive overlap of conditions and the high incidence of low HDL cholesterol highlight the urgent need for comprehensive medical and lifestyle interventions.

The initial significant study on Rosuvastatin in India was the ROSUVEES study.[39] This study explored the link between high levels of low-density lipoprotein cholesterol (LDL-C) and increased cardiovascular risk, underscoring the effectiveness of rosuvastatin in reducing LDL-C levels. Previous clinical research has indicated that rosuvastatin can decrease LDL-C levels by 39 to 56%, with 71 to 89% of patients reaching their LDL-C targets. This makes it more effective compared to other statins such as atorvastatin, simvastatin, and pravastatin. Furthermore, rosuvastatin has been shown to enhance levels of high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1, triglycerides (TG), and improve the LDL-C:HDL-C ratio. However, India lacks studies comparing the clinical outcomes of different doses of rosuvastatin in hyperlipidemic patients. Therefore, the ROSUVEES study aimed to fill this gap by providing country-specific information to optimize therapeutic regimens with rosuvastatin for hyperlipidemic patients in India, ensuring they meet the recommended lipid goals. The study was an 8-weeks, open-label, non-randomized, parallel-group, post-marketing study conducted across 14 centers in three cities in India. Patients were prescribed rosuvastatin at starting doses of 5, 10, or 20 mg based on clinical judgment and considering baseline LDL-C levels, future cardiovascular risk, potential adverse reactions, and the recommendations in the package insert. The study included men and women aged 18 to 65 years with hypercholesterolemia and fasting LDL-C levels >130 mg/dL requiring lipid-altering therapy. Those with specific conditions or on certain medications were excluded. The study found that all three doses of rosuvastatin significantly reduced LDL-C, triglycerides, VLDL, and total cholesterol levels from baseline. A high percentage of patients reached the National Cholesterol Education Program-defined LDL-C and non-HDL goals for their risk category, particularly those at higher cardiovascular risk taking the 10 or 20 mg doses. Rosuvastatin was well-tolerated, with few reported adverse events. The study concludes that rosuvastatin is an effective and safe option for reducing LDL-C levels in Indian patients with hyperlipidemia, and emphasizes the importance of country-specific information in tailoring therapeutic regimens to improve clinical outcomes in lipid and cardiovascular risk management.

The ROSUVEES - 2 study, +6 published the following year, reported that intensive therapy with rosuvastatin at a dose of 40 mg/day significantly reduced LDL-C, total cholesterol (TC), triglycerides, TC/high-density lipoprotein cholesterol (HDL-C) ratio, non-HDL-C, LDL-C/HDL-C ratio, and high-sensitivity C-reactive protein (hsCRP) levels in both very high-risk and high-risk patients with ACS. Specifically, rosuvastatin lowered mean LDL-C by 40.5 mg/dL, and 54.5% of patients reached their LDL-C goal of <70 mg/dL after 12 weeks of treatment.

The study also assessed the safety and tolerability of rosuvastatin, reporting few adverse events including muscle pain (myalgia). These events led to dose adjustment in 8 patients, but none were classified as serious, and there were no deaths during the study. These findings are consistent with previous clinical trials, confirming that rosuvastatin is generally well-tolerated with a positive safety profile. This study demonstrates the efficacy of high-dose rosuvastatin in reducing LDL-C levels in Indian patients with ACS who are at high risk of cardiovascular disease.

Current Guidelines and Recommendations for Statin Use in ACS

Lipid-lowering therapy, particularly with statins, plays a crucial role in cardiovascular disease management, although its mechanisms of action are not fully understood. LDL cholesterol is known to cause regression of atherosclerosis; however, the benefits of statin therapy are observed within months of initiation, which is too soon for regression to be the primary cause. Statins are believed to stabilize atherosclerotic plaques, thereby reducing the likelihood of plaque rupture and subsequent thrombotic events such as heart attacks or strokes.[40,41] They also exhibit anti-inflammatory properties that can mitigate the inflammatory responses within the plaques and vascular walls, further preventing plaque rupture. Moreover, statins have been shown to improve endothelial function, which is crucial for maintaining healthy blood vessels. In patients with ACS, lipid-lowering therapy has been linked to a reduction in cardiac deaths. Furthermore, studies involving patients with implantable cardioverter-defibrillators have shown a decrease in life-threatening ventricular arrhythmias with statin therapy.[42]

Based on the robust evidence, current guidelines recommend early initiation of high-intensity statin therapy in patients with ACS irrespective of baseline LDL-C levels.[43] This approach is advocated to maximize the pleiotropic and cholesterol-lowering effects of statins, potentially translating into improved outcomes. The intensity of statin therapy is classified into two main categories: moderate-intensity and high-intensity.[44] Moderate-intensity statin therapy aims to achieve a 30 to 50% reduction in LDL-C levels. Examples of daily dosages for moderate-intensity statin therapy include:

- Lovastatin: 40 to 80 mg
- Pravastatin: 40 to 80 mg

- Simvastatin: 20 to 40 mg
- Atorvastatin: 10 to 20 mg
- Rosuvastatin: 5 to 10 mg
- Pitavastatin: 2 to 4 mg

On the other hand, high-intensity statin therapy aims for a reduction of LDL-C levels by 50% or more. Daily dosage examples for high-intensity statin therapy include:

- Atorvastatin: 40 to 80 mg
- Rosuvastatin: 20 to 40 mg.

In-hospital therapy for ACS patients involves a targeted approach to lowering low-density lipoprotein cholesterol (LDL-C) levels to approximately 50 mg/dL (1.29 mmol/L). Initiating LDL-C lowering therapy promptly following diagnosis is essential.

For those with a baseline LDL-C of ≥55 mg/dL (1.29 mmol/L) prior to statin treatment, high-intensity statin therapy is advised, consisting of 80 mg of atorvastatin or 20 to 40 mg of rosuvastatin daily, to be continued indefinitely.

Patients already on a moderate-dose statin should have their therapy intensified. For those receiving high-intensity statin treatment, the addition of ezetimibe 10 mg daily is recommended. If the LDL-C goal of 50 mg/dL (1.29 mmol/L) is unlikely to be reached with ezetimibe, consideration of a PCSK9 (PCSK9 stands for proprotein convertase subtilisin kexin type 9) inhibitor during hospitalization is reasonable.

In cases where the baseline LDL-C is significantly high (>160 mg/dL [4.14 mmol/L]), such that achieving an LDL-C of <70 mg/dL (1.81 mmol/L) with high-intensity statin treatment is unlikely, ezetimibe should be started alongside the high-intensity statin therapy. After initiating or continuing the statin, the LDL-C level should be rechecked in 4 to 6 weeks.

For the rare patient with a baseline LDL-C of <50 mg/dL (1.29 mmol/L) before statin therapy, there is no specific recommendation regarding statin therapy due to lack of data. It is suggested to recheck LDL-C levels to confirm accuracy and consider other risk factors contributing to the coronary event, such as lipoprotein(a) excess. For patients with a baseline LDL-C of <50 mg/dL (1.29 mmol/L), moderate-intensity statin therapy is recommended.

CONCLUSION

High-intensity statin therapy has been a fundamental aspect of lipid-lowering treatment in ACS for the past two decades, offering both early and long-term benefits. The typical approach involves treating with high-intensity statins, specifically atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg daily, with a preference for the highest approved dose in most cases. Among the available options, Rosuvastatin has shown superior efficacy in lowering lipid levels and promoting plaque regression when compared to Atorvastatin. However, it's important to note that this superiority in efficacy has not yet translated into a significant improvement in cardiovascular outcomes. Furthermore, there is a note of caution regarding the potential for new-onset diabetes mellitus associated with high-dose Rosuvastatin use. In patients who are intolerant to high-intensity statin therapy, it is recommended a combination of moderate-intensity statin plus ezetimibe. Despite the differences in efficacy and potential risks, current guidelines do not distinguish between Rosuvastatin and Atorvastatin for clinical use, leaving the choice largely up to individual clinicians and patient-specific considerations.

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How to cite this article: Gupta P, Mani UA, Kumar M, Abbas H. High Intensity Statins in Acute Coronary Syndrome Part 2: A comparison of Atorvastatin and Rosuvastatin for use in ACS, Clinical trials in India and Place for statins in current guidelines. Hypertens J. 2023; 9(2): 39-44.
Source of support: Nil, **Conflicts of interest:** None