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Review Article

High-Intensity Statins in Acute Coronary Syndrome Part I: A look at the Pharmacological Properties of Statins and Clinical Trials on Statins in ACS.

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Abstract

Acute coronary syndrome (ACS) is a term that encompasses a range of conditions associated with sudden, reduced blood flow to the heart. These conditions can range from unstable angina to myocardial infarction. Over the years, various therapeutic agents have been utilized to manage ACS and improve clinical outcomes. One of the mainstays of therapy for ACS has been the class of medications known as statins. We discuss the role of statins in ACS, their mechanism of action, clinical evidence supporting their use, and the potential future directions in this area. This critical period post-ACS underscores the necessity for effective interventions to mitigate further risks. Among the therapeutic options available, statins play a pivotal role. These medications, when administered soon after an ACS event, offer significant benefits. Statins have the potential to stabilize atherosclerotic plaques, reduce the lipid component of these plaques, and decrease inflammation—all of which contribute to reducing the risk of subsequent cardiac events. Given the elevated risk immediately after an ACS event, it becomes imperative to initiate statin therapy as early as possible to ensure the maximum reduction in potential adverse outcomes. The timely introduction of statins can thus provide pronounced benefits during the period when the patient's risk is at its peak.

Keywords: Acute Coronary Syndrome, Statins.

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Mechanism of Action of Statins

Statins, or HMG-CoA reductase inhibitors, primarily function by inhibiting the enzyme HMG-CoA reductase. This enzyme plays a pivotal role in the mevalonate pathway, which is responsible for cholesterol synthesis in the liver. By inhibiting this enzyme, statins decrease the levels of cholesterol, specifically low-density lipoprotein cholesterol (LDL-C).[1]

However, in the context of ACS, the pleiotropic effects of statins are of notable interest. These are beneficial effects beyond cholesterol-lowering and include improving endothelial function, stabilization of atherosclerotic plaques, and reduction in inflammation.[2,3] Such actions can significantly mitigate the risk of a subsequent cardiovascular event in ACS patients.

Statins play a crucial role in inhibiting the enzyme responsible for endogenous cholesterol synthesis in the liver. This reduction in cholesterol synthesis leads to an upregulation of LDL-receptors activity.[4] As a result of the increased presence of these receptors, the liver enhances its uptake of VLDL-LDL-cholesterol, leading to reduced levels of these cholesterol types in the bloodstream. Additionally, statins promote an elevation in HDL (High-Density Lipoprotein), often considered the 'good cholesterol'.[5]

One of the primary concerns with cholesterol is the formation of atherogenic lipoproteins such as VLDL, IDL, and LDL. These lipoproteins contribute to the development of plaque in blood vessels, increasing the risk of atherosclerosis. By reducing the levels of these atherogenic lipoproteins, statins mitigate the risk associated with plaque buildup. Furthermore, statins have a balancing effect on atherosclerotic plaques by promoting cholesterol efflux or the removal of cholesterol from plaques. This is achieved through the increased production of HDL and enhanced catabolism of ApoB Lps, leading to the regression of plaque. As a consequence of these actions, there's a noted reduction in the cholesterol content of plaques and an enhancement in their stability. Ultimately, these multifaceted effects of statins result in a decreased occurrence of cardiovascular events, including heart attacks and strokes, emphasizing their importance in cardiovascular health.

Statins are renowned for their cholesterol-lowering capabilities, but their impact goes well beyond this primary function, especially concerning endothelial cells. The core action of statins lies in inhibiting the enzyme HMG-CoA reductase, which plays a pivotal role in

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cholesterol synthesis. This inhibition brings forth a cascade of events: Lymphocytes, a type of white blood cell, have a surface molecule called LFA-1. Statins selectively obstruct the interaction between LFA-1 and ICAM-1, leading to decreased lymphocyte adhesion and activity. This modulation can have anti-inflammatory implications within the blood vessels. Concurrently, by inhibiting HMG-CoA reductase, statins also affect the synthesis of isoprenoids like Geranylgeranyl PP and Farnesyl PP.[6] These compounds are crucial for the prenylation of proteins such as Rho. With the reduced availability of these isoprenoids, the prenylation of Rho protein declines, resulting in its diminished activity. This decrease in Rho activity subsequently elevates the transcription of NOS mRNA, the blueprint for Nitric Oxide Synthase.[7] This enzyme is responsible for producing nitric oxide (NO) in endothelial cells. The action of statins doesn't stop here; they further bolster NO production by enhancing the stability of NOS mRNA.

The role of NO is paramount for vascular health. It aids in expanding blood vessels and exhibits anti-inflammatory properties. Elevated NO production, spurred by statins, curtails the adhesion of monocytes to the endothelial lining, reducing the inflammation within vessels. On the other hand, LDL cholesterol can undergo oxidation to form oxLDL. Statins, by lowering LDL levels, can potentially decrease the formation of oxLDL. This is vital as oxLDL can deactivate NO, negating its positive effects.

Furthermore, statins influence the NF-κB pathway, a central signaling mechanism in inflammation. Their effect leads to diminished activation of NF-κB, thereby attenuating the inflammatory response. Thus, while the primary acclaim of statins revolves around cholesterol management, their multifaceted impact on endothelial cell functions, inflammatory processes, and overall vascular health underscores their significance in managing cardiovascular diseases.

The process of thrombus (blood clot) formation is intricate and involves multiple factors and stages. When a plaque ruptures, tissue factor (TF) is expressed. Tissue factor then interacts with Factor VII to form the Factor VII-TF complex.[8] This complex plays a crucial role in activating Factor X, turning it into Factor Xa.[9]

In another branch of the coagulation pathway, Factor V gets activated and transformed into Factor Va. Factor Xa and Factor Va work in tandem to convert prothrombin, an inactive zymogen, into its active form, thrombin. Thrombin is a pivotal enzyme in the clotting process. It facilitates the transformation of fibrinogen, a soluble protein, into fibrin polymer. As fibrin polymers form, Factor XIII assists in converting these into cross-linked fibrin, strengthening the clot structure.

Simultaneously, thrombin also promotes platelet aggregation, which aids in the fortification and growth of the thrombus. Consequently, the net effect of these combined processes leads to thrombus formation, which can potentially block blood vessels, leading to conditions such as heart attacks or strokes.

Statins, typically known for their cholesterol-lowering properties, also exhibit antithrombotic properties. Statin therapy can influence various stages of the clotting cascade. For instance, statin therapy can decrease tissue factor expression, inhibit Factor V activation, decrease factor XIII mediated fibrin cross-linkages and platelet aggregation thereby suppressing thrombin generation.[10] By intervening at these key junctures, statins can mitigate the risk of thrombus formation, emphasizing their multifaceted therapeutic benefits beyond cholesterol management.

Endothelial dysfunction is a pathological state where the endothelium (inner lining) of blood vessels fails to perform its normal functions, leading to vascular complications. This dysfunction can manifest as a paradoxical constriction in response to stimuli that would typically induce dilation.[11] Factors such as serotonin, ADP, thrombin, and low intra-coronary pressure are some contributors that can promote this aberrant behavior. In such a dysfunctional state, levels of atherogenic particles like VLDL, IDL, and LDL can rise, exacerbating the problem.[12,13] High levels of these lipoproteins in the bloodstream are associated with a heightened risk of atherosclerosis and other cardiovascular diseases.

The introduction of statin therapy offers a beneficial intervention in this scenario. They can counter the detrimental effects of the dysfunctional endothelium. Post statin intervention, the endothelium exhibits adaptive dilation, a healthier response to stimuli. The levels of atherogenic lipoproteins, namely VLDL, IDL, and LDL, are also decreased in the presence of statins, while the beneficial HDL remains unaffected.

Consequently, with statin treatment, the endothelium transitions from a dysfunctional state to a normalized function, effectively restoring vascular health and reducing the risk of cardiovascular complications.[4] This therapeutic action underlines the importance of statins in cardiovascular medicine beyond just cholesterol management.

Statins play a multifaceted role in the context of acute coronary syndromes (ACS). They interact with various components and processes in the cardiovascular system. Some of their effects include improving endothelial function, modulating platelet activation, affecting reactive oxygen species, and influencing the action of nitrous oxide. Moreover, they also interact with coagulation pathways, have an impact on endothelial progenitor cells, and affect collagen and matrix metalloproteinases (MMPs). In addition, statins also interface with the AT1 Receptor and vascular smooth muscle cells (VSMC), impacting their proliferation. Macrophage inflammation and immunomodulation are also areas where statins showcase their influence.

Key mechanistic roles of statins, especially in relation to ACS, include the potential to stabilize atherosclerotic plaques, which is pivotal in preventing catastrophic cardiovascular events(14). They can also reduce the lipid component of coronary plaques, making the plaques less prone to rupture. A significant attribute of statins is their potential to markedly reduce the incidence of plaque rupture, a primary event leading to myocardial infarction.

In summary, statins exhibit a broad range of positive impacts on cardiovascular health, especially in the context of ACS, by targeting various pathways and cell types. This goes beyond their primary known role in lowering cholesterol, underscoring their importance in cardiovascular therapeutics.

The dyslipidemia pattern predominantly observed in the Indian population has been characterized by three major features. Firstly, there is an elevated level of small dense LDL (sd-LDL) cholesterol. Secondly, there is a notable increase in VLDL (Very Low-Density Lipoprotein)

cholesterol levels. Lastly, this pattern is accompanied by decreased levels of HDL (High-Density Lipoprotein) cholesterol. A central aspect interconnecting these lipid irregularities is insulin resistance. Insulin resistance can lead to an increase in the production of VLDL cholesterol, which in turn is associated with higher sd-LDL levels.[15] Moreover, insulin resistance is also linked to reduced HDL cholesterol levels.

Several landmark trials have established the efficacy of statins in ACS:

The MIRACL Study: Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering.[16]

This trial assessed the role of atorvastatin in patients with ACS. Patients treated with atorvastatin exhibited a significant reduction in the risk of a recurrent ischemic event within the first 16 weeks post-ACS. It focused on the effects of early-initiated atorvastatin (80 mg) following an acute coronary syndrome (ACS) on death and recurrent ischemic events. The study design was multicenter, randomized, double-blind, and placebo-controlled. Patients were assigned to receive atorvastatin (80 mg) or a placebo within 24 to 96 hours after their hospital admission for an acute coronary syndrome. The study had a sample size of 3,086 participants. The primary endpoint of the study was a composite of several adverse outcomes including death, non-fatal acute myocardial infarction (MI), cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia that required emergency rehospitalization. Group receiving atorvastatin had a lower incidence of these events compared to the placebo group. Specifically, the atorvastatin group had a 14.8% incidence rate, while the placebo group had a 17.4% incidence rate. This translates to a 16% relative risk reduction with a hazard ratio (HR) of 0.84 (with a 95% confidence interval of 0.70 to 0.99) and a p-value of 0.048, suggesting that the difference is statistically significant. The primary outcome of interest was the occurrence of death and/or nonfatal acute myocardial infarction (MI). In the placebo group, 10.9% of the patients experienced this outcome, while in the Atorvastatin group, 10.1% faced a similar outcome. This translated to a relative risk (RR) of 0.92 when taking Atorvastatin as compared to the placebo.

Breaking down the primary outcome further, the risk of death had an RR of 0.94, nonfatal acute MI had an RR of 0.90, resuscitated cardiac arrest was at 0.82, and recurrent symptomatic myocardial ischemia, which required emergency rehospitalization, showed a reduced RR of 0.74.

Several secondary outcomes were also evaluated. The risk of experiencing a stroke and nonfatal events was halved (RR = 0.50) in the Atorvastatin group. For coronary revascularization, the RR was 1.02. Percutaneous coronary interventions had an RR of 1.06, surgical interventions were at 0.97, and worsening angina without new objective evidence of ischemia was at 0.86. Additionally, the occurrence of new or worsening congestive heart failure that necessitated rehospitalization had an RR of 0.94 in the Atorvastatin group.

Finally, when considering any primary or secondary outcome, 29.3% of patients in the placebo group and 28.0% in the Atorvastatin group were affected. The associated RR for these combined outcomes was 0.95. It's also noteworthy that the mean LDL cholesterol level for those on Atorvastatin was 72 mg/dL. When interpreting these results, it's essential to consider both the statistical significance and the clinical relevance of the observed differences. In a safety analysis of two groups of patients, one receiving a placebo and the other Atorvastatin, various adverse events were examined. For both groups, the incidence of any serious adverse event was less than 1%. However, there were differences observed in the incidence of elevated liver transaminases (greater than 3 times the upper limit of normal). The placebo group had a 0.6% occurrence rate, while the Atorvastatin group showed a rate of 2.5%. This difference was statistically significant with a P value of less than 0.001. In terms of myositis, an inflammatory condition of the muscles, there was no observed occurrence in either group. The data indicates the importance of monitoring liver function in patients receiving Atorvastatin, given the elevated risk observed in comparison to placebo. In conclusion, for patients diagnosed with stable coronary heart disease (CHD) who also present with acute coronary syndrome (ACS), initiating early lipid-lowering treatment using atorvastatin at a dosage of 80 mg/day has demonstrated benefits. Specifically, this therapeutic approach has been associated with a reduced risk of two major cardiovascular events. First, the likelihood of early recurrent ischemic events, especially those characterized by recurrent symptomatic ischemia that necessitates rehospitalization, is diminished. Secondly, the therapy also decreases the risk of experiencing either a non-fatal or fatal stroke.

The PROVE IT-TIMI 22 Trial: PRavastatin Or AtorVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22.[17]

This study compared intensive statin therapy (atorvastatin 80 mg) to standard therapy (pravastatin 40 mg) in ACS patients. The results highlighted that intensive statin therapy led to a greater reduction in the risk of death or major cardiovascular events. The "PROVE IT: TIMI 22" trial investigated the effects of intensive versus moderate lipid-lowering therapy using statins following an acute coronary syndrome (ACS) event. The study specifically compared the outcomes of patients treated with atorvastatin 80 mg, targeting an LDL cholesterol level of less than 1.60 mmol/L, to those treated with pravastatin 40 mg, aiming for an LDL level of less than 2.46 mmol/L. Designed as a randomised, double-blind, double-dummy non-inferiority trial, the study followed participants for an average of 24 months.

The primary endpoints of the study were encompassed the incidence of death from any cause, myocardial infarction (MI), documented unstable angina leading to hospitalization, revascularization procedures, and stroke. In addition, secondary endpoints included assessing the risk of death from coronary heart disease (CHD), the occurrence of non-fatal MI, the necessity for revascularization, and the risk of death from CHD or a non-fatal MI. The insights from the "PROVE IT: TIMI 22" trial were crucial in guiding medical decisions regarding the optimal choice of statin therapy and desired LDL levels for patients post-ACS. Over a follow-up period that extended up to 30 months, the event rate for the pravastatin group was 26.3%, while the atorvastatin group had a rate of 22.4%.

The results indicate a 16% relative risk reduction (RRR) in the atorvastatin group compared to the pravastatin group. This difference is statistically significant, with a hazard ratio (HR) of 0.84 and a confidence interval ranging from 0.74 to 0.95. The p-value, which measures the

statistical significance, is 0.005. This suggests that the difference between the two groups is likely not due to chance. Major CV events considered in the study encompassed myocardial infarction (MI), documented cases of unstable angina that required hospitalization, revascularization procedures (either through percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) if conducted at least 30 days after randomization), and strokes.

For the pravastatin 40 mg group, the LDL-C levels initially showed a noticeable decline from the baseline, reaching their lowest point around 4 months. After this point, the levels begin to rise again, though they remain lower than the baseline levels. In contrast, the atorvastatin 80 mg group exhibits a pronounced drop in LDL-C levels within the initial 30 days. These levels stay relatively consistent and low throughout the duration of the study. Furthermore, the study indicates a 21% decrease in LDL-C levels for the pravastatin 40 mg group and a more significant 49% reduction for the atorvastatin 80 mg group. Notably, the atorvastatin 80 mg treatment achieved a median LDL-C level of 62 mg/dL, a result that's statistically significant with a p-value of less than 0.001. In essence, both treatments effectively lowered LDL-C levels, with atorvastatin 80 mg demonstrating a more substantial and sustained reduction compared to pravastatin 40 mg.

In a safety comparison between Atorvastatin 80 mg and Pravastatin 40 mg, various parameters were assessed. When it came to the discontinuation of the medication due to adverse events or other reasons such as patient preference, Atorvastatin had a rate of 30.4%, while Pravastatin stood at 33.0%. The difference between these rates wasn't statistically significant, as indicated by a *p-value* of 0.11. In terms of discontinuation due to muscle pain or CK elevation, 3.3% of patients on Atorvastatin discontinued, compared to 2.7% on Pravastatin, with a P value of 0.23. Interestingly, neither group reported any cases of rhabdomyolysis. Another parameter assessed was the ALT levels, specifically levels greater than three times the upper normal limit. For Atorvastatin users, this was observed in 3.3% of the patients, whereas it was only 1.1% for Pravastatin users. This difference was found to be statistically significant with a *p-value* of less than 0.001. Finally, when considering the rate at which the medication dose was reduced due to side effects or raised liver function tests, Atorvastatin had a rate of 1.9%, and Pravastatin had a rate of 1.4%, with a *p-value* of 0.20, indicating no significant difference between the two groups.

In conclusion 'Intensive' lipid-lowering with 80 mg atorvastatin to a median LDL-C of 1.6 mmol/L was associated with a significant reduction in the risk of combined all-cause mortality and major CV events by 16% compared to 'moderate' lipid-lowering therapy with 40 mg pravastatin which achieved a median LDL-C of 2.5 mmol/L (p=0.005). Initiating intensive statin treatment promptly after an ACS can decrease clinical events within the first 30 days, likely due to enhanced early pleiotropic effects. In patients with stable conditions, this rigorous statin treatment offers prolonged clinical event reduction compared to regular treatment. Therefore, it's advisable to begin ACS patients on intensive statin treatment during their hospital stay and maintain it for an extended period.[18]

In 2006 a meta-analysis was performed on 13 important randomized controlled trials which concluded that early intensive statin therapy for ACS decreased the rate of death and cardiovascular events by 20% over 2 years of follow-up and benefit start early by 4 -12 months, achieving statistical significance by 12 months (19). A similar Meta-analysis performed in 2020 supported the above findings with 23% reduction in major adverse cardiac events across 16 studies noting a higher reduction in Asian subjects.[20]

The Position of Rosuvastatin

Rosuvastatin is a synthetic HMG-CoA reductase inhibitor. It belongs to a new generation characterized by methane-sulphonamide pyrimidine and N-methane sulfonyl pyrrole-substituted 3, 5-dihydroxy-heptenoates. Rosuvastatin's binding capacity for the enzyme's active site is quadruple that of HMG-CoA's affinity for the enzyme. Its high binding capacity, combined with a firm ionic connection, leads to a prolonged duration for enzyme activity restoration after Rosuvastatin is removed. Rosuvastatin demonstrates a heightened affinity for OATP-IBI, which contributes to its enhanced efficacy when contrasted with other statins, evident in its ability to decrease LDL-C and TG levels and Its role in enhancing HDL-C and the ApoB:ApoA-I ratio. Rosuvastatin has a bioavailability of 20%, meaning that after administration, 20% of the drug becomes available in the bloodstream. The drug's peak concentration, referred to as T_{max}, is achieved in 5 hours post-administration. Furthermore, 90% of this drug has an affinity to bind with proteins present in the bloodstream. In terms of its duration in the body, the half-life of the drug is 19 hours, signifying that it takes this duration for its concentration to reduce by half. Interestingly, when it comes to excretion, 90% of the drug is eliminated from the body unchanged and is expelled through the feces. An additional highlight is the drug's comparatively lower potential for interacting with other drugs, distinguishing it from certain other statins. Another notable feature of Rosuvastatin is its versatility in terms of intake. It can be consumed with or without food and is suitable for administration either in the morning or evening.

The GALAXY programs: Pioneering Progress in Statin Therapy for CVD

The emergence of cardiovascular diseases (CVD) as the leading cause of mortality globally necessitated effective therapeutic strategies. In this context, the GALAXY programs stand as a landmark initiative aimed at evaluating the role of statins, specifically rosuvastatin, in the management of CVD.

Spanning a range of clinical trials and observational studies, the GALAXY programs primarily aimed to understand the potential of rosuvastatin in various patient subgroups, contrasting risk scenarios, and across diverse ethnic populations. A distinct characteristic of these programs was their inclusivity, considering both primary and secondary prevention targets and patients from varying clinical backgrounds.[21,22]

The results from the GALAXY suite of studies have been pivotal in elucidating the benefits of rosuvastatin. They demonstrated the drug's efficacy in LDL-cholesterol reduction, its role in stabilizing atherosclerotic plaques, and its favorable safety profile compared to other statins. Moreover, the findings significantly influenced guidelines for statin therapy, enhancing our approach toward CVD management.

Table 1 – Summary of some important trials and studies done on Rosuvastatin.

Study	Acronym	Conclusion of the study
ASTEROID[23]	A study to evaluate the effect of Rosuvastatin on Intravascular ultrasound-derived coronary atheroma burden	Very high-intensity statin therapy using rosuvastatin 40 mg/d achieved an average LDL-C of 60.8 mg/dL and increased HDL-C by 14.7%, resulting in significant regression of atherosclerosis for all 3 prespecified Intravascular Ultrasound measures of disease burden. Treatment to LDL-C levels below currently accepted guidelines, when accompanied by significant HDL-C increases, can regress atherosclerosis in coronary disease patients.
AURORA[24]	A study evaluating the use of Rosuvastatin in patients requiring ongoing renal dialysis: An assessment of survival and cardiovascular events	In patients undergoing hemodialysis, the initiation of treatment with rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
CENTAURUS[25,26]	Comparison of the effects noted in the ApoB/ApoA-I ratio using rosuvastatin and atorvastatin in patients with ACUte coronary Syndrome	In patients with non-ST-elevation acute coronary syndrome, rosuvastatin 20 mg decreased apoB/apoA-1 ratio at 1-month more than atorvastatin 80 mg. No difference could be shown at 3 months; thus, the primary endpoint was not met.
COMETS[27]	A Comparative study with rosuvastatin in subjects with METabolic Syndrome	At equivalent doses, rosuvastatin had a significantly greater effect than atorvastatin in lowering LDL-C and improving the lipid profile and was well tolerated in patients with the metabolic syndrome.
CORONA[28]	COntrolled Rosuvastatin multiNAtional study in heart failure	When repeat events were included, rosuvastatin was shown to reduce the risk of HFH by approximately 15% to 20%, equating to approximately 76 fewer admissions per 1,000 patients treated over a median 33 months of follow-up. Including repeat events could increase the ability to detect treatment effects in heart failure trials.
COSMOS[29]	COronary atherosclerosis study measuring effeCts Of rosuvastatin using intravascular ultrasound in Japanese subjects	Rosuvastatin exerted significant regression of coronary plaque volume in Japanese patients with stable CAD, including those who had previously used other lipid-lowering drugs. Rosuvastatin might be useful in the setting of secondary prevention in patients with stable CAD.
DISCOVERY Program[30]	Direct Comparison of low-density lipoprotein cholesterol Values: an Evaluation of Rosuvastatin therapY	Rosuvastatin 10 mg is significantly more effective at achieving NCEP ATP III and European LDL-C goals, lowering LDL-C and TC in both naïve and switched patients and increasing HDL-C in naïve patients than atorvastatin 10 mg, with a similar safety and tolerability profile. This study also provides evidence regarding the comparative effects of rosuvastatin versus atorvastatin in Latin American and Portuguese populations.
ECLIPSE[31]	An Evaluation to Compare Lipid-lowering effects of rosuvastatin and atorvastatin In force-titrated subjects: a prospective study of efficacy and tolerability	Rosuvastatin titrated across its recommended dose range provides a more favorable effect on lipoprotein variables than atorvastatin, enabling more high-risk patients to achieve recommended LDL-C goals.
EXPLORER[32]	Examination of Potential Lipid modifying effects Of Rosuvastatin in combination with Ezetimibe versus Rosuvastatin alone	rosuvastatin plus ezetimibe may improve the management of high-risk patients who cannot achieve goal on maximal statin monotherapy.

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Study	Acronym	Conclusion of the study
JUPITER[33]	Justification for the Use of statins in primary prevention: an Intervention Trial Evaluating Rosuvastatin	For people choosing to start pharmacological prophylaxis, reduction in both LDL cholesterol and hsCRP are indicators of successful treatment with rosuvastatin.
LUNAR[34]	Limiting UNdertreatment of lipids in Acute coronary syndrome	RSV40 is potentially a more favorable choice over ATV80, especially for those who haven't been able to reach a target LDL-C level below 70 mg/dL with their previous statin treatment. Additionally, for individuals whose baseline LDL-C levels indicate that they might not reach the target LDL-C of under 70 mg/dL while on ATV80, RSV40 becomes a more advisable option.
MERCURY I[35,36]	Measuring effective Reductions in cholesterol using Rosuvastatin therapY	Rosuvastatin 10 mg reduces lipid ratios more than equivalent and higher doses of other statins; switching to equal or lower doses of rosuvastatin produces significantly improved reductions in lipid ratios.
MERCURY 2[37]	Measuring effective Reductions in Cholesterol using Rosuvastatin therapY	Rosuvastatin 10 or 20 mg is an effective and safe therapeutic option for high-risk patients to achieve their lipid and apolipoprotein targets.
METEOR[38]	Measuring effects on intima-media thickness: an evaluation of Rosuvastatin	In middle-aged adults with a Framingham Risk Score of less than 10% and evidence of subclinical atherosclerosis, rosuvastatin resulted in statistically significant reductions in the rate of progression of maximum Carotid Intima Medial Thickness over 2 years vs placebo. Rosuvastatin did not induce disease regression.
ORBITAL Program[39]	Open-label primary care study: Rosuvastatin-based compliance Initiatives linked To Achievement of Low-density lipoprotein goals	Rosuvastatin 10/20 mg daily enables the majority of patients to achieve LDL-C less than 115 mg/dL within 3 months. The compliance-enhancing program was only effective in statin-naive patients at early time points but had no overall effect over 12 months.
PULSAR[40]	Prospective study to evaluate the Utility of Low doses of the Statins Atorvastatin and Rosuvastatin	In high-risk patients with hypercholesterolemia, rosuvastatin 10 mg was more efficacious than atorvastatin 20 mg at reducing LDL-C, enabling LDL-C goal achievement and improving other lipid parameters. Both treatments were well tolerated.
ROMA[41]	A non-Galaxy trial	High loading dose of rosuvastatin within 24 hours before elective PCI seems to decrease the incidence of periprocedural myocardial necrosis during a period of 12 months compared to the standard treatment.
SATURN[42]	Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin	Maximal doses of rosuvastatin and atorvastatin resulted in significant regression of coronary atherosclerosis. Despite the lower level of LDL cholesterol and the higher level of HDL cholesterol achieved with rosuvastatin, a similar degree of regression of Percent Atheroma Volume was observed in the two treatment groups.
STELLAR[43]	Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin	Rosuvastatin was more effective at reducing LDL-C, improving the lipid profile, and enabling more patients to achieve goals including the updated 2003 European and 2004 NCEP LDL-C goals, compared with other statins at equivalent or lower doses.
URANUS[44]	Use of Rosuvastatin versus Atorvastatin in type 2 diabetes mellitus	At the start dose and following dose titration, rosuvastatin was significantly more effective than atorvastatin at reducing LDL-C and achieving European LDL-C goals in patients with type 2 diabetes.

Conclusion

Statins have emerged as a cornerstone in the management of ACS. Their ability to lower cholesterol, stabilize vulnerable plaques, and exert anti-inflammatory effects positions them as invaluable agents in reducing the risk of subsequent cardiovascular events in ACS patients. As research continues, further nuances in statin therapy, such as personalized approaches based on genetic profiles or ACS subtypes, may further refine their role in this clinical context. In the second part we shall discuss "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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