

Safety Profile of Atorvastatin and Rosuvastatin: Significance of Pharmacovigilance Signal Detection

Yash Goel¹, Prithpal Singh Matreja²

¹Research Scholar, Department of Pharmacology, TMMC&RC, Teerthanker Mahaveer University, Moradabad (U.P), India

Email: 619yashg@gmail.com

²Professor, Department of Pharmacology, TMMC&RC, Teerthanker Mahaveer University, Moradabad (U.P), India

Corresponding Author: Yash Goel, Research Scholar, Department of Pharmacology, TMMC&RC, Teerthanker Mahaveer University, Moradabad (U.P), India

Email: 619yashg@gmail.com

Abstract

Statins are the cornerstone of lipid-lowering therapy for the prevention of cardiovascular diseases. Among them, atorvastatin and rosuvastatin are widely prescribed high-intensity statins due to their potent efficacy in reducing low-density lipoprotein cholesterol (LDL-C) and cardiovascular morbidity and mortality. Despite their overall favorable safety profile, statins are associated with adverse drug reactions (ADRs) affecting musculoskeletal, hepatic, metabolic, neurological, and gastrointestinal systems. Pre-marketing clinical trials may not adequately detect rare, delayed, or population-specific adverse effects, highlighting the importance of post-marketing pharmacovigilance.

This review evaluates and compares the safety profiles of atorvastatin and rosuvastatin with particular emphasis on pharmacovigilance signal detection. A narrative review of literature published between 2000 and 2025 was conducted using electronic databases including PubMed, Scopus, Web of Science, Embase, and Google Scholar. Pharmacovigilance databases such as the FDA Adverse Event Reporting System (FAERS) and WHO Vigibase were also examined. Studies including pharmacovigilance analyses, randomized controlled trials, observational studies, and systematic reviews assessing statin safety were included. Signal detection methods such as reporting odds ratio (ROR) and proportional reporting ratio (PRR) were reviewed to identify disproportionate reporting of adverse drug reactions.

Available evidence indicates that both statins have favorable benefit–risk profiles; however, pharmacokinetic differences influence their safety patterns. Atorvastatin, a lipophilic statin extensively metabolized by CYP3A4, shows stronger signal associations with hepatotoxicity, diabetes mellitus, and neurological adverse effects. Rosuvastatin, a hydrophilic statin with greater hepatoselectivity and minimal cytochrome P450 metabolism, demonstrates relatively lower systemic adverse effects. Pharmacovigilance signal detection plays a crucial role in identifying rare adverse drug reactions, improving drug safety monitoring, and supporting individualized statin therapy.

Keywords: Atorvastatin, Rosuvastatin, Pharmacovigilance, Signal Detection, Adverse Drug Reactions, Drug Safety, Reporting Odds Ratio

How to cite this article: Goel Y, Matreja PS. Safety Profile of Atorvastatin and Rosuvastatin: Significance of Pharmacovigilance Signal Detection. *Int J Drug Deliv Technol.* 2026;16(6s): 954-959; DOI: 10.25258/ijddt.16.6s.124

Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, accounting for approximately 17.9 million deaths annually and representing a major global public health burden.¹ Dyslipidemia, particularly elevated low-density lipoprotein cholesterol (LDL-C), is a major modifiable risk factor contributing to the development and progression of atherosclerosis, which underlies coronary artery disease, stroke, and peripheral vascular

disease.² Effective management of dyslipidemia is therefore essential for reducing cardiovascular risk and improving clinical outcomes.

Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are the most widely prescribed lipid-lowering agents due to their well-established efficacy and safety profile.³ These drugs act by inhibiting HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis, resulting in decreased intracellular cholesterol

production and upregulation of LDL receptors on hepatocytes.⁴ This mechanism enhances clearance of circulating LDL cholesterol and significantly reduces plasma LDL levels. In addition to lipid-lowering effects, statins exhibit pleiotropic effects including anti-inflammatory activity, improved endothelial function, and stabilization of atherosclerotic plaques, which contribute to their cardiovascular protective effects.⁵

Among available statins, atorvastatin and rosuvastatin are classified as high-intensity statins due to their ability to reduce LDL-C levels by more than 50%.⁶ These statins are widely used in both primary and secondary prevention of cardiovascular disease due to their superior efficacy and favorable pharmacokinetic properties. Large clinical trials such as the Treating to New Targets (TNT) study and the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) demonstrated significant reductions in cardiovascular events with atorvastatin and rosuvastatin therapy.^{7,8}

Despite their favorable benefit-risk profile, statins are associated with adverse drug reactions that may affect patient compliance and clinical outcomes.⁹ Common adverse effects include muscle-related symptoms such as myalgia and myopathy, hepatic enzyme elevations, gastrointestinal disturbances, and neurological symptoms.¹⁰ Rare but serious adverse effects include rhabdomyolysis and severe hepatotoxicity.¹¹ Statin therapy has also been associated with an increased risk of new-onset diabetes mellitus, particularly with high-intensity statin therapy.¹²

Pre-marketing clinical trials are essential for evaluating drug safety; however, they have limitations in detecting rare, delayed, or population-specific adverse drug reactions due to limited sample size and duration.¹³ Additionally, clinical trial populations may not fully represent real-world patients with multiple comorbidities and concomitant medications.¹⁴ Therefore, post-marketing pharmacovigilance is critical for monitoring drug safety in real-world settings.

Pharmacovigilance involves the detection, assessment, and prevention of adverse drug reactions using spontaneous reporting databases such as FAERS and WHO Vigibase.¹⁵ Signal detection methods such as reporting odds ratio (ROR) and proportional reporting ratio (PRR) enable identification of potential associations between drugs and adverse events.¹⁶ Pharmacovigilance signal detection has contributed significantly to identifying safety concerns associated with statins and improving patient safety.

This review aims to comprehensively evaluate the safety profiles of atorvastatin and rosuvastatin and highlight the importance of pharmacovigilance signal detection in improving drug safety and optimizing clinical decision-making.

Methodology

This study was conducted as a narrative review of the published literature to evaluate and compare the safety profiles of atorvastatin and rosuvastatin, with a particular focus on pharmacovigilance data and signal detection methods related to adverse drug reactions (ADRs). The World Health Organization defines ADR's as "a response to a medication that is noxious and unintended and occurs at doses normally used in man."¹⁷ A comprehensive literature search was performed across multiple electronic databases including PubMed, Scopus, Web of Science, Embase, and Google Scholar to identify relevant publications. In addition to traditional literature sources, major pharmacovigilance databases such as the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) and the World Health Organization global database, Vigibase, were also examined to capture reported adverse drug reaction signals associated with statin therapy. The search included studies published between January 2000 and March 2025.

The search strategy incorporated a combination of keywords and medical subject headings related to statins and drug safety. The primary search terms included "atorvastatin," "rosuvastatin," "statins," "adverse drug reactions," "pharmacovigilance," "signal detection," "reporting odds ratio," and "drug safety." These terms were used individually and in combination using Boolean operators to ensure comprehensive retrieval of relevant literature. Studies were included if they evaluated the safety profile, adverse drug reactions, or pharmacovigilance signals associated with atorvastatin or rosuvastatin. Eligible study designs included pharmacovigilance analyses, randomized controlled trials, observational studies, cohort studies, case-control studies, and systematic reviews that reported safety outcomes related to statin use. Articles not published in English, conference abstracts without full text, and studies lacking relevant safety data were excluded.

Particular emphasis was placed on studies utilizing pharmacovigilance signal detection methodologies. The principal disproportionality analysis methods reviewed included the Reporting Odds Ratio (ROR) and the Proportional Reporting Ratio (PRR). In

pharmacovigilance analysis, a signal was considered present when the ROR was greater than 1 or when the PRR was greater than or equal to 2, suggesting a disproportionate reporting of a specific adverse event associated with the drug of interest.¹⁶

Relevant studies were screened and reviewed to identify reported adverse events, safety signals, and comparative safety outcomes between atorvastatin and rosuvastatin. The findings from the selected literature were then synthesized narratively to provide an overview of the pharmacovigilance evidence related to statin safety.

Review of Literature

Pharmacological Characteristics

Atorvastatin is classified as a lipophilic (fat-soluble) statin. This chemical property allows it to easily diffuse across cell membranes, resulting in extensive metabolism primarily driven by the hepatic CYP3A4 enzyme system. While effective, this lipophilicity facilitates a much wider distribution throughout extrahepatic (peripheral) tissues, which inherently increases its potential to cause systemic adverse effects and drug-drug interactions.¹⁸ Conversely, rosuvastatin is a hydrophilic (water-soluble) statin. This structural difference grants it significantly greater hepatoselectivity—meaning it preferentially targets the liver where cholesterol synthesis occurs—and ensures it undergoes minimal cytochrome P450 (CYP) metabolism. As a result, rosuvastatin produces far lower systemic exposure in peripheral tissues.¹⁹ These fundamental pharmacokinetic differences are the primary drivers behind the distinct variations observed in their respective safety profiles. A detailed description is shown in Figure 1.

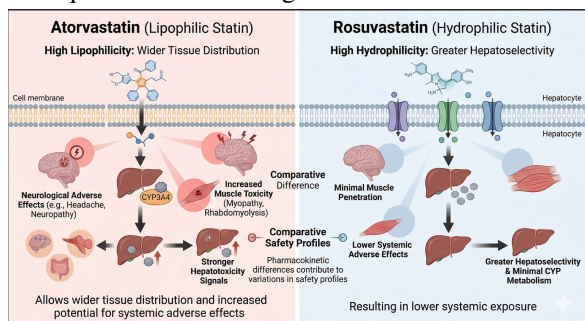


Figure 1: Comparative Pharmacokinetics and Safety Profiles of Atorvastatin vs. Rosuvastatin

Musculoskeletal Safety Profile

Muscle-related toxicity remains the most frequently reported adverse effect associated with statin therapy. This toxicity presents on a clinical spectrum ranging from mild myalgia (muscle aches without enzyme elevation) and myopathy (muscle weakness) to severe, potentially fatal rhabdomyolysis (muscle

breakdown).²⁰ The underlying pathophysiological mechanism driving this damage is largely believed to involve statin-induced mitochondrial dysfunction within muscle cells, which impairs cellular energy production and may be linked to the depletion of coenzyme Q10.²¹ Comprehensive signal detection studies utilizing post-marketing databases have consistently demonstrated an increased rate of reporting for muscle toxicity with both atorvastatin and rosuvastatin.²² However, because lipophilic statins such as atorvastatin readily penetrate extrahepatic cell membranes, they achieve greater concentrations in muscle tissue, leading to a theoretically higher and more frequently observed risk of muscle toxicity compared to hydrophilic alternatives.¹⁸

Hepatic Safety Profile

Because statins exert their primary mechanism of action and undergo extensive metabolism within the liver, they are well-documented to cause asymptomatic elevations in liver transaminases (liver enzymes).²³ Ongoing signal detection studies analyzing adverse event registries have successfully identified robust hepatotoxicity signals associated with the use of both atorvastatin and rosuvastatin.²⁴ Notably, atorvastatin consistently demonstrates stronger, more pronounced hepatotoxicity signals, a phenomenon largely attributed to its heavy reliance on the CYP enzyme system for hepatic clearance, which can place a higher metabolic burden on the liver.²⁵

Metabolic Safety Profile

In recent clinical evaluations, statin therapy has been independently associated with a dose-dependent increased risk of developing incident diabetes mellitus, potentially by altering insulin sensitivity and beta-cell secretion.¹² Advanced signal detection studies specifically evaluating this metabolic risk have demonstrated markedly increased diabetes risk signals associated with the use of atorvastatin when directly compared to rosuvastatin, suggesting a distinct metabolic profile between the two drugs.²⁶

Neurological Safety Profile

While less common than musculoskeletal or hepatic issues, statins are capable of causing a variety of neurological adverse effects, most notably including headaches, peripheral neuropathy, and occasionally sleep disturbances or cognitive fuzziness.²⁷ Because highly lipophilic statins such as atorvastatin possess the necessary chemical properties to cross the blood-brain barrier far more easily than hydrophilic statins, they exert a more direct pharmacological effect on the central nervous system.¹⁸ Consequently, signal detection studies reveal significantly stronger and more

frequent neurological adverse effect signals for atorvastatin compared to its counterparts.²⁸

Gastrointestinal Safety Profile

Patients frequently report gastrointestinal adverse effects upon initiating or titrating statin therapy. The most commonly reported gastrointestinal symptoms include nausea, constipation, diarrhea, and dyspepsia (indigestion).²⁹ Fortunately, in routine clinical practice, these adverse effects are usually mild, transient in nature, and can often be managed effectively without discontinuing the medication.

Role of Pharmacovigilance Signal Detection

Pharmacovigilance signal detection plays a critical, ongoing role in post-marketing drug safety. By systematically analyzing large, spontaneous reporting databases (such as the FDA's FAERS), researchers can identify previously unrecognized or emerging adverse drug reactions.¹⁵ The statistical methods utilized to quantify these safety signals rely on disproportionality analysis, most notably including:

Reporting Odds Ratio (ROR): An estimate of the relative risk of an adverse event occurring with a specific drug compared to all other drugs in the database.

Proportional Reporting Ratio (PRR): A measure of how frequently an adverse event is reported for a specific drug relative to the reporting frequency of that same event for all other drugs.

Together, these mathematical models help epidemiologists detect mathematically significant drug-safety signals that warrant further regulatory review.

Comparative Safety Profile

When summarizing the overall comparative safety profile, atorvastatin consistently demonstrates stronger post-marketing signal associations with several critical adverse events. Most notably, these include:

Diabetes mellitus (new-onset)

Hepatotoxicity (transaminase elevations)

Neurological adverse effects (due to central nervous system penetration)

Conversely, rosuvastatin generally demonstrates a much lower propensity for broad systemic adverse effects. This superior systemic safety profile is primarily due to its hydrophilic structure and high hepatoselectivity, which effectively restricts its pharmacological activity mostly to the liver.¹⁹

Clinical Implications

To actively mitigate these risks and ensure therapeutic efficacy, clinicians must implement proactive monitoring strategies for all patients on statin therapy. Key clinical practices include monitoring:

Liver function: Obtaining baseline transaminase levels before initiation and checking them if symptoms of hepatotoxicity arise.

Muscle symptoms: Educating patients to report unexplained muscle pain or weakness, and checking creatine kinase (CK) levels if myopathy is suspected.

Blood glucose levels: Routinely screening fasting blood glucose or HbA1c, particularly in patients with predisposing risk factors for diabetes.

Ultimately, robust pharmacovigilance data combined with individualized clinical monitoring drastically improves overall patient safety and long-term cardiovascular outcomes.

Limitations

This review has several limitations. As a narrative review, the study relies on previously published literature and pharmacovigilance data, which may be subject to reporting bias, underreporting, and incomplete clinical information. Spontaneous reporting systems such as FAERS and Vigibase cannot establish causal relationships between drugs and adverse events, and the data may be influenced by confounding factors such as comorbidities, concomitant medications, and variations in reporting practices. In addition, heterogeneity among included studies and differences in study design, patient populations, and outcome measures may limit direct comparison of safety outcomes between atorvastatin and rosuvastatin.

Future Directions

Future research should focus on large-scale pharmacoepidemiological studies and real-world evidence to further clarify the comparative safety profiles of statins across diverse populations. The integration of advanced pharmacovigilance methodologies, including machine learning and artificial intelligence-based signal detection, may enhance early identification of adverse drug reactions. Prospective studies evaluating genetic susceptibility, pharmacogenomics, and patient-specific risk factors may also facilitate personalized statin therapy. Strengthening global pharmacovigilance reporting systems and encouraging active adverse event reporting will further improve the detection and management of statin-associated adverse drug reactions and ultimately enhance patient safety.

Conclusion

Atorvastatin and rosuvastatin are among the most widely prescribed high-intensity statins and play a critical role in the management of dyslipidemia and prevention of cardiovascular diseases. Both agents demonstrate strong efficacy in lowering LDL-

cholesterol and reducing cardiovascular morbidity and mortality. Overall, these statins possess a favorable benefit–risk profile; however, differences in their pharmacokinetic and pharmacodynamic properties influence their safety patterns. Evidence from pharmacovigilance and clinical studies indicates that atorvastatin, being a lipophilic statin extensively metabolized by the CYP3A4 enzyme system, shows stronger associations with certain adverse drug reactions, including hepatotoxicity, new-onset diabetes mellitus, and neurological effects. In contrast, rosuvastatin, a hydrophilic statin with greater hepatoselectivity and minimal cytochrome P450 metabolism, generally demonstrates lower systemic exposure and a comparatively reduced risk of systemic adverse effects.

Pharmacovigilance signal detection plays a pivotal role in identifying rare, delayed, and previously unrecognized adverse drug reactions that may not be detected during pre-marketing clinical trials. Analytical methods such as reporting odds ratio (ROR) and proportional reporting ratio (PRR) enable early identification of potential safety signals from large pharmacovigilance databases such as FAERS and WHO Vigibase. These approaches contribute significantly to improving drug safety monitoring, guiding regulatory decisions, and supporting individualized treatment strategies in clinical practice.

References

1. World Health Organization. Global cardiovascular statistics 2023. Geneva: World Health Organization; 2023.
2. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. *Eur Heart J*. 2017;38(32):2459–2472.
3. Endo A. A historical perspective on the discovery of statins. *J Lipid Res*. 2010;51(1):3–8.
4. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. *Nature*. 1990;343(6257):425–430.
5. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. *Circulation*. 2004;109(23 Suppl 1):III39–III43.
6. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA cholesterol treatment guideline. *Circulation*. 2014;129(25 Suppl 2):S1–S45.
7. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in stable coronary disease. *N Engl J Med*. 2005;352(14):1425–1435.
8. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women. *N Engl J Med*. 2008;359(21):2195–2207.
9. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. *J Am Coll Cardiol*. 2016;67(20):2395–2410.
10. Armitage J. The safety of statins in clinical practice. *Lancet*. 2007;370(9601):1781–1790.
11. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, et al. Incidence of hospitalized rhabdomyolysis with statin use. *N Engl J Med*. 2004;350(6):539–549.
12. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes. *Lancet*. 2010;375(9716):735–742.
13. Strom BL, Kimmel SE, Hennessy S. *Pharmacoepidemiology*. 6th ed. Chichester: Wiley-Blackwell; 2019.
14. Eichler HG, Abadie E, Breckenridge A, Flamion B, Gustafsson LL, Leufkens H, et al. Bridging the efficacy-effectiveness gap. *Nat Rev Drug Discov*. 2011;10(7):495–506.
15. World Health Organization. WHO pharmacovigilance guidelines. Geneva: World Health Organization; 2023.
16. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios for signal generation. *Pharmacoepidemiol Drug Saf*. 2001;10(6):483–486.
17. Joseph G, Bhatti N, Badyal DK, Kaur P. Stevens–Johnson syndrome: An adverse drug reaction with various drugs. *Indian J. Physiol. Pharmacol*. 2025;69(3):1–4.
18. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins. *Fundam Clin Pharmacol*. 2005;19(1):117–125.
19. McTaggart F. Comparative pharmacology of atorvastatin and rosuvastatin. *Eur Heart J Suppl*. 2003;5(Suppl F):F12–F18.
20. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms. *Eur Heart J*. 2015;36(17):1012–1022.

21. Bouitbir J, Charles AL, Echaniz-Laguna A, Kindo M, Daussin F, Auwerx J, et al. Mechanisms of statin-associated muscle toxicity. *Eur J Clin Invest.* 2019;49(2):e13064.
22. Raschi E, Poluzzi E, Salvo F, Pariente A, Antonazzo IC, De Ponti F. Pharmacovigilance of statins. *Drug Saf.* 2017;40(2):123–135.
23. Björnsson E. Hepatotoxicity associated with statins. *Hepatology.* 2012;56(1):374–380.
24. Zhai C, Cong H, Zhang Y, Liu Y, Liu X. Signal detection of statin-associated adverse drug reactions. *Front Pharmacol.* 2023;14:1145678.
25. Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of statin adverse events. *Biol Pharm Bull.* 2011;34(11):1716–1720.
26. Casula M, Mozzanica F, Scotti L, Tragni E, Pirillo A, Corrao G, et al. Statin use and risk of diabetes. *Diabetes Care.* 2017;40(12):164–170.
27. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss. *Pharmacotherapy.* 2003;23(7):871–880.
28. Tuccori M, Lapi F, Testi A, Coli D, Moretti U, Vannacci A, et al. Statin-associated psychiatric adverse events. *Drug Saf.* 2014;37(11):983–992.
29. Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, et al. Risks associated with statin therapy. *Circulation.* 2006;114(25):2788–2797.