J Lipid Atheroscler. 2024 Jan;13(1):61-68
https://doi.org/10.12997/jla.2024.13.1.61
pISSN 2287-2892·eISSN 2288-2561

JLA Journal of Lipid and Atherosclerosis

Original Article

Check for updates

Statins Ticagrelor and Rhabdomyolysis: A Coincidence or a Drug Interaction?

Ramesh Patel [1], **Jai Bharat Sharma** [1], **Saraswati Rajput** [2]

[1]Department of Cardiology, Geetanjali Medical College and Hospital, Udaipur, India
[2]Department of Medicine, Geetanjali Medical College and Hospital, Udaipur, India

OPEN ACCESS

Received: May 8, 2023
Revised: Aug 8, 2023
Accepted: Sep 9, 2023
Published online: Oct 26, 2023

Correspondence to
Jai Bharat Sharma
Department of Cardiology, Geetanjali Medical College and Hospital, Hiranmagri Extension, Manwakhera NH-8 Bypass, Near Eklingpura, Chouraha, Udaipur 313001, India.
Email: Jai561989igmc@gmail.com

ORCID iDs
Ramesh Patel
https://orcid.org/0009-0009-0856-1279
Jai Bharat Sharma
https://orcid.org/0000-0002-8344-2060
Saraswati Rajput
https://orcid.org/0009-0003-7101-5285

Funding
None.

Conflict of Interest
The authors have no conflicts of interest to declare.

Data Availability Statement
The datasets generated during and/or analyzed during the current study are available

ABSTRACT

Objective: Statins play a key role in the management of atherosclerotic cardiovascular disease for both primary and secondary prevention. However, their increasing usage has correspondingly led to a higher incidence of adverse effects, with muscle symptoms being the most common. An intriguing drug interaction exists between ticagrelor and high-intensity statins, which may exacerbate the adverse effects of statin-induced rhabdomyolysis, leading to significant consequences. This study was conducted to examine the profile of patients who have experienced statin-induced rhabdomyolysis while undergoing percutaneous transluminal coronary angioplasty (PTCA).
Methods: This was an observational study that included 1,862 patients who underwent PTCA at our institute over the course of 1 year.
Results: Over a 1-year period, we encountered four patients who were being treated with high-intensity statin therapy following acute coronary syndrome. These patients presented with muscle weakness and kidney injury. A notable commonality among all patients was the co-prescription of ticagrelor. Two patients died, while the other 2 were successfully managed through hydration, electrolyte balance, dialysis, and alternative lipid management drugs.
Conclusion: The concomitant use of ticagrelor and high-intensity statins should be carefully considered due to the additional risk of rhabdomyolysis and kidney injury. Future pharmacokinetic studies are needed to establish a causal relationship and predict potential drug interactions, which, if not avoided, could be fatal.

Keywords: Statins; Rhabdomyolysis; Drug interactions; Adverse drug reactions; Ticagrelor

INTRODUCTION

In the Indian subcontinent, atherosclerotic cardiovascular disease (ASCVD) tends to present a decade earlier and follows a more malignant course. In this context, statins are a cornerstone of our treatment strategy. An anticipated increase in statin usage is expected due to the ASCVD epidemic, further driven by improvements in health infrastructure, a growing understanding of clinical lipidology, and more aggressive low-density lipoprotein cholesterol (LDL-C) goals.[1,2] However, this increase will also likely lead to a rise in the incidence of statin-related adverse effects. These can include muscle symptoms, acute kidney injury, hepatitis,

from the corresponding author on reasonable request.

Author Contributions

Conceptualization: Patel R, Sharma JB; Data curation: Patel R, Rajput S; Investigation: Sharma JB, Rajput S; Methodology: Sharma JB; Project administration: Patel R; Resources: Sharma JB; Supervision: Patel R; Writing - original draft: Sharma JB, Rajput S; Writing - review & editing: Sharma JB.

fulminant liver failure, new-onset diabetes mellitus, gastrointestinal discomfort, peripheral neuropathy, insomnia, and neurocognitive dysfunction. Statin-associated muscle symptoms are the most common adverse events and can range from subjective myalgias without muscle enzyme elevation, to severe myopathy and weakness with muscle enzyme elevation, and even to the most severe form of rhabdomyolysis with acute kidney injury, which can be fatal.[3-5]

The incidence of rhabdomyolysis, while relatively rare, ranges from 0.6 to 1.2 per 10,000 person-years with the use of currently available statins. However, as more patients are prescribed statins, the cumulative burden is likely to increase.[6] Another reason to exercise caution regarding this severe adverse reaction is the potential drug interaction of statins, particularly with ticagrelor. This interaction has been reported in a limited number of case studies and warrants further investigation, especially as the concurrent use of ticagrelor and statins is on the rise. This increase is due to ticagrelor becoming off-patent, which has led to a cost reduction of more than 50%, thereby increasing its usage.[7] In this report, we present a series of patients who developed statin-induced rhabdomyolysis, two of whom succumbed to the illness.

MATERIALS AND METHODS

In this case series, we observed statin-induced rhabdomyolysis in 4 patients over a 1-year period. These patients were part of a larger group of 1,862 percutaneous transluminal coronary angioplasty (PTCA) patients, among whom 936 were concurrently using ticagrelor.

RESULTS

1. Case 1

A 48-year-old male patient with hypertension and a body mass index (BMI) of 24.1 kg/m^2 was admitted due to generalized weakness, limb pain, and stiffness. These symptoms had gradually developed and worsened over a 3-week period. He also reported experiencing oliguria, nausea, and vomiting for the past week. His medical history included hypertension and a previous inferior wall myocardial infarction (MI). Four months prior, he underwent primary PTCA on his right coronary artery (RCA). His current medications included aspirin, ticagrelor, high-intensity rosuvastatin (40 mg), ramipril, and metoprolol. Upon examination, the patient exhibited tachypnea, tachycardia, and pitting edema. His lower limbs were tender, and he had diminished stretch reflexes in both his upper and lower limbs. No other significant findings were noted during the examination of other systems. Admission investigations revealed the following: hemoglobin, 15.4 g/dL; total leukocyte count (TLC), 12,700/mL; platelet count, 2.37 ×10^5/mL; erythrocyte sedimentation rate (ESR), 2 mm in the first hour; urea, 187.3 mg/dL; creatinine, 9.96 mg/dL (at the time of discharge after PTCA, creatinine was 1.1 mg/dL with an estimated glomerular filtration rate [eGFR] of 71 mL/min/1.73 m^2); calcium, 8.7 mg/dL; phosphorus, 9.17 mg/dL; sodium, 126 mEq/L; potassium, 5.56 mEq/L; total / direct bilirubin, 1.11/0.56 mg/dL; serum glutamic-oxaloacetic transaminase (SGOT), 1,401 U/L; serum glutamic-pyruvic transaminase (SGPT), 606 U/L; alkaline phosphatase (ALP), 192 IU/L; international normalized ratio (INR), 1.3; magnesium, 4 mg/dL; antinuclear antibodies (ANA), negative; low 25-OH vitamin D levels (13 ng/mL); thyroid-stimulated hormone (TSH), 8.37 mIU/L; T4, 8.4 ug/dL; T3, 1.28 ng/mL; creatine phosphokinase (CPK), 18,970 U/L; urine protein, ++; blood, +; no red blood cells (RBCs) per high-powered field (HPF) on microscopy; lactate dehydrogenase (LDH), 373.5 U/L.

https://doi.org/10.12997/jla.2024.13.1.61

Electromyography (EMG) and nerve conduction velocity (NCV) studies suggested myositis. The patient was diagnosed with rhabdomyolysis, acute kidney injury, 25-OH vitamin D deficiency, and acute hepatic injury.

He was managed with the discontinuation of statins, the administration of hemodialysis, the use of steroids, the correction of electrolyte imbalances, the adjustment of vitamin D levels, and the provision of symptomatic treatment. Over a period of two weeks, the patient's condition gradually improved. After 5 sessions of hemodialysis, the patient was discharged. During the follow-up, we initiated a lipid management regimen for the patient, which included the use of ezetimibe. The patient is currently undergoing follow-up. After 6 months, his condition is stable and his kidney functions have improved, with his most recent eGFR measuring 73 mL/min/1.73 m^2.

2. Case 2

A 70-year-old female patient with hypertension and diabetes, and a BMI of 26.4 kg/m^2, was admitted due to an ST elevated inferior wall MI. She was on moderate-intensity statins (atorvastatin 10 mg). Coronary angiography (CAG) revealed double vessel disease (DVD), which was managed with PTCA to the RCA. Upon discharge, she was prescribed aspirin, ticagrelor, high-dose statins (rosuvastatin 40 mg), ramipril, and oral hypoglycemics (glimepiride, metformin and voglibose) and insulin. One week later, she returned with generalized myalgias. A physical examination revealed tenderness in all four limbs, a power rating of 2/5, and depressed stretch reflexes in both the upper and lower limbs. No remarkable findings were noted in other system examinations. Her laboratory results were as follows: hemoglobin, 12.4 g/dL; TLC, 17,700/mL; platelet, 2.01 ×10^5/mL; ESR, 13 mm in the 1st hour; urea, 190 mg/dL; creatinine, 3.28 mg/dL (previous post-percutaneous coronary intervention creatinine, 1.2 mg/dL with eGFR, 49 mL/min/1.73m^2); calcium, 8.9 mg/dL; phosphorus, 5.97 mg/dL; sodium, 117 mEq/L; potassium, 5.1 mEq/L; total / direct bilirubin 0.91 / 0.33 mg/dL; SGOT, 129 U/L; SGPT, 214 U/L; ALP, 154 IU/L; INR, 1.5; low 25-OH vitamin D levels (16 ng/mL); CPK, 10,850 U/L; urine protein, ++; blood, +; 3-4 RBC/HPF; LDH, 415 U/L. EMG and NCV were done and suggested myositis. The patient was diagnosed with rhabdomyolysis, acute kidney injury, and vitamin D deficiency.

The patient's management included the discontinuation of statins, the administration of steroids, correction of electrolyte imbalances, and vitamin D supplementation, along with symptomatic treatment. She remained stable for a period of 3 weeks. However, she subsequently experienced a severe, acute gastrointestinal bleed and died.

3. Case 3

A 67-year-old male with diabetes and dyslipidemia, and a BMI of 24.5 kg/m^2, was admitted due to acute coronary syndrome (anterior wall MI). He was on a moderate-intensity statin (atorvastatin 10 mg). Coronary angiography revealed single-vessel disease, which was managed with PTCA to the left anterior descending (LAD) artery. Upon discharge, he was prescribed aspirin, ticagrelor, high-dose statins (atorvastatin 80 mg), diuretics, beta blockers, and glimepiride. Two weeks later, he presented with shortness of breath and anasarca. The patient's examination revealed tachypnea, tachycardia, a blood pressure of 160/90 mmHg, edema, and elevated jugular venous pressure. Other systemic examinations were unremarkable. Laboratory investigations revealed the following: hemoglobin, 13.9 g/dL; TLC, 57,400/mL; platelet, 1.91 ×10^5/mL; ESR, 23 mm in the first hour; urea, 290 mg/dL; creatinine, 8.62 mg/dL (post-PTCA creatinine: 0.9 mg/dL with an eGFR of 94 mL/min/1.73 m^2); calcium, 9.1 mg/dL; phosphorus,

https://doi.org/10.12997/jla.2024.13.1.61

9.17 mg/dL; sodium, 121 mEq/L; potassium, 5.9 mEq/L; total / direct bilirubin 1.29 / 0.30 mg/dL; SGOT, 117 U/L; SGPT, 133 U/L; ALP, 116 IU/L; INR, 1.42; total cholesterol, 131 mg/dL; LDL-C, 61 mg/dL; 25-OH vitamin D levels, normal; CPK, 36,011 U/L; urine protein, +++; blood, +; no RBC/HPF; LDH, 422 U/L. EMG and NCV were suggestive of myositis. The patient was diagnosed with rhabdomyolysis accompanied by acute kidney injury.

The patient's management involved discontinuing statins, administering steroids, correcting electrolyte imbalances, and providing hemodialysis and symptomatic treatment. After 4 weeks, the patient showed improvement and is currently stable at CKD stage IIIa (eGFR 48 mL/min/1.73 m^2). An alternative lipid-lowering drug, ezetimibe, was introduced.

4. Case 4

A 74-year-old woman with hypertension and no diabetes was admitted due to acute coronary syndrome (unstable angina IIIB1). She had normal left ventricular systolic function, and a CAG revealed DVD, which was managed with PTCA to the LAD and left circumflex artery. She was discharged on aspirin, ticagrelor, rosuvastatin (40 mg), ramipril, and beta-blockers, and her recovery was uneventful. One month later, she presented with generalized myalgia, decreased urine output, and altered behavior. Upon examination, the patient had tender limbs with a power of 3/5 and depressed stretch reflexes in both upper and lower limbs. The examination of other systems was unremarkable. Her laboratory investigations revealed the following: hemoglobin, 11.1 g/dL; TLC, 19,300/mL; platelet, 2.22 ×10^5/mL; ESR, 19 mm in the 1st hour; urea, 216 mg/dL; creatinine, 6.28 mg/dL (post-PTCA creatinine: 1.0 mg/dL with an eGFR of 59 mL/min/1.73 m^2); calcium, 8.9 mg/dL; phosphorus, 5.17 mg/dL; sodium, 113 mEq/L; potassium, 5.41 mEq/L; total / direct bilirubin 1.41 / 0.43 mg/dL; SGOT, 159 U/L; SGPT, 163 U/L; ALP, 164 IU/L; INR, 1.6; low 25-OH vitamin D levels (29 ng/mL); CPK, 40,205 U/L; urine protein, +; blood, +; 1-2 RBC/HPF; LDH, 425 U/L. EMG and NCV could not be performed due to the patient's malignant course. She was diagnosed with rhabdomyolysis and acute kidney injury.

The patient's treatment involved discontinuing statins, administering steroids, correcting electrolyte imbalances, and performing hemodialysis. Despite these efforts, the patient's condition deteriorated and she died on the third day of her hospital stay.

DISCUSSION

In this case series, we observed 4 patients who developed statin-induced rhabdomyolysis over a 1-year period. These patients were among 1,862 PTCA patients, 936 of whom were also using ticagrelor. This sparked our interest in a possible interaction, as none of our patients were on an alternative P2Y12 inhibitor, and the occurrence of rhabdomyolysis was higher than usual.[6] The use of ticagrelor has surged in India following the off-patenting of the molecule and a reduction in cost by the country's pricing agency. This may necessitate further investigation into this interaction, which could lead to potentially fatal complications. Notably, the PLATO trial documented significantly worse renal function in patients taking ticagrelor than in those taking clopidogrel. Serum creatinine increased by 30% in 25.5% of patients receiving ticagrelor, and 8.3% of these patients experienced an increase in creatinine by more than 50%, highlighting the renal implications of ticagrelor.[8]

Multiple pathophysiological mechanisms contribute to the myotoxicity of statins. Statins inhibit the formation of mevalonate, which is not only a precursor of cholesterol but

https://doi.org/10.12997/jla.2024.13.1.61

also of other isoprenoid intermediary metabolites. These metabolites play a role in the post-translational lipid modification of proteins and their functions. Statins can lead to membrane hyperexcitability associated with impaired chloride conductance.[9] Mevalonate is also a precursor of coenzyme Q10, an essential cofactor of the electron transport chain, and therefore, mitochondrial functions may be impaired.[10]

Several demographic or health-related factors may predispose an individual to develop statin-induced rhabdomyolysis. These factors include older age, frailty, multisystem diseases, and the use of multiple medications. Conditions such as hypothyroidism, vitamin D deficiency, impaired liver function, and impaired kidney function are also believed to increase the incidence of statin-induced myopathy.[11] In our series (**Table 1**), older age (with a mean age of 64.75 years and a standard deviation of 9.98), vitamin D deficiency, high doses of statins, and polypharmacy were likely significant risk factors for rhabdomyolysis and associated mortality. However, the death in the second case could potentially be attributed to the use of a platelet inhibitor, although renal and hepatic injuries may have also contributed to the severity of the condition.

Ticagrelor was a striking commonality in all cases under consideration. It has been previously reported that ticagrelor competes with statins during metabolism by CYP 3A4, which leads to statin retention and can precipitate rhabdomyolysis and renal failure.[12] However, other noteworthy explanations have been proposed in the literature over the years. Three potential mechanisms have been described in the literature regarding how ticagrelor might influence the elimination or disposition of rosuvastatin. The first is that ticagrelor may cause renal impairment. This is speculated to occur due to ticagrelor's inhibition of adenosine reuptake, which reduces the glomerular filtration rate by causing vasoconstriction of the afferent renal arterioles. This, in turn, leads to decreased renal excretion of rosuvastatin. The second proposed mechanism is competition at the transporter level (OATP1B1, P-glycoprotein, ABCG2, MRP2), which results in decreased biliary and renal excretion of the statin. The third mechanism involves genetic polymorphism of metabolic enzymes (cytochromes P450, UDP-glucuronosyltransferases) and drug transporters, which leads to increased competition between drugs.[13,14] Atorvastatin has also been implicated in various reports in a similar manner.[15]

Weakness and muscle pain within 1 month of initiating statin treatment were the most common symptoms observed in our patients. These symptoms are also reported in more

Table 1. Characteristics of patients with statin-induced rhabdomyolysis

Patient characteristic	Case 1	Case 2	Case 3	Case 4
Age (yr)	48	70	67	74
Sex	Male	Female	Male	Female
Previous statin dose	None	Atorvastatin 10 mg	Atorvastatin 10 mg	None
DM	No	Yes	Yes	No
Prior eGFR, mL/min/1.73 m^2 (mg/dL)	71 (1.1)	49 (1.2)	94 (0.9)	59 (1)
BMI (kg/m^2)	24.1	26.4	24.5	Not available
Current statin and dose	Rosuvastatin 40 mg	Rosuvastatin 40 mg	Atorvastatin 80 mg	Rosuvastatin 40 mg
Antiplatelet	Ticagrelor 90 mg twice daily	Ticagrelor 90 mg twice daily	Ticagrelor 90 mg twice daily	Ticagrelor 90 mg twice daily
Symptom onset time (wk)	13	1	2	4
Peak CK level (U/L)	18,970	10,850	36,011	40,205
LDH level (U/L)	373	415	422	425
25-OH vitamin D (ng/mL)	13	16	43	29
Peak creatinine (mg/dL)	9.96	3.28	8.62	6.28
Outcome	Survival	Death	Survival	Death

DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; BMI, body mass index; CK, creatine kinase; LDH, lactate dehydrogenase.

https://doi.org/10.12997/jla.2024.13.1.61

than 60% of patients in the literature, followed by other symptoms such as inability to walk, dark urine, fatigue, malaise, shortness of breath, nausea, muscle tenderness, and flaccid muscles.[1] The course of the illness can be fatal, with an overall mortality rate of 15% reported in some studies. Higher mortality rates were observed in older individuals (56–75 years), a finding that aligns with our study.[12,16] In a study by Mendes et al.,[16] 15 of the 17 reported deaths occurred in male patients, whereas in our series, both patients who died were women. Clinicians should be aware that statin-induced rhabdomyolysis can occur in patients who have been stable for some time, particularly if the statin dosage is altered, a new medication is introduced that can enhance the statin's potency, or there is a change in the patient's exercise status. Autoimmune-mediated necrotizing myositis is a severe form of rhabdomyolysis that can occur after statin therapy. However, due to the unavailability of the 3-hydroxy-3-methylglutaryl-CoA reductase antibody assay at our center, we consider it a rare possibility in the differential diagnosis. Rhabdomyolysis is typically treated with intravenous rehydration or dialysis for patients with more severe symptoms. After evaluating a patient's condition, a lower dose of statin may still be used. If a patient develops rhabdomyolysis due to the administration of lipophilic statins, such as atorvastatin and simvastatin, it may be reasonable to switch to hydrophilic statins, such as pravastatin and rosuvastatin. However, alternative lipid-lowering drugs such as ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and bempedoic acid provide other viable options.[17] Another approach may be to transition from ticagrelor to clopidogrel and use a different statin or lower dose. However, we preferred a stronger antiplatelet in view of acute coronary syndrome, and we plan to switch to clopidogrel with a gradual introduction of statins in the future. The use of PCSK9 inhibitors is limited in our area due to availability and financial constraints.

Another significant concern in our series was the high intensity and dosage of the statin used. Various studies have suggested that Asians can achieve similar benefits to those of the Western population at lower statin doses, which may be a way to avoid dose-related side effects. However, the relationship between dosage and rhabdomyolysis has not yet been established in studies.[18] Specifically for South Asians, pharmacokinetic studies suggest that Indians achieve 1.68 times the plasma level of rosuvastatin compared to the Caucasian population when administered a single 40 mg dose of rosuvastatin.[19] A study conducted in a region of Southern India revealed the presence of the *SLCO1B1* C allele, a risk factor for statin-induced myopathy due to reduced statin uptake by the liver, in 15% of the population. This suggests an increased propensity for statin-induced myopathy in certain South Asian groups.[20] However, a study by Gupta et al.[21] evaluating the effects of statins on LDL-C and HDL-C in South Asians and whites suggested that South Asians should be treated with statin doses similar to those used for whites. This opens up the possibility for further studies on pharmacokinetic interactions, particularly given the increasing use of statins, ticagrelor, and co-prescribed drugs in the context of the ASCVD epidemic.[1]

This case series underscores the importance of maintaining a high level of suspicion for statin-induced rhabdomyolysis, which can have fatal consequences if not detected and managed promptly. The concurrent use of ticagrelor and statins may elevate the typical rate of fatal adverse drug complications associated with statin-induced rhabdomyolysis. The significance of being aware of drug interactions due to polypharmacy and comorbidities should not be underestimated. The interaction between ticagrelor and statins warrants careful consideration and further evaluation to establish causality. Physicians should be cognizant of these potentially lethal combinations and permutations, which can be managed with appropriate early diagnosis. With alternative lipid-lowering drugs, patients who cannot tolerate statins can

https://doi.org/10.12997/jla.2024.13.1.61

be effectively managed without the need to reintroduce statins. Our intention is to alert the medical community to this potentially fatal interaction between statins and ticagrelor, which are often used simultaneously in the management of ASCVD. However, we do not wish to undermine the proven value of ticagrelor in reducing cardiovascular mortality following acute coronary syndrome. This case series appears to us to be a hypothesis-generating series in the post-marketing surveillance of ticagrelor and certainly warrants further research.

REFERENCES

1. Duell PB, Mehta V, Nair D, Puri S, Nanda R, Puri R. The epidemic of atherosclerotic cardiovascular disease in India. J Clin Lipidol 2020;14:170-172. PUBMED | CROSSREF
2. Liu Y, Lv X, Xie N, Fang Z, Ren W, Gong Y, et al. Time trends analysis of statin prescription prevalence, therapy initiation, dose intensity, and utilization from the hospital information system of Jinshan Hospital, Shanghai (2012-2018). BMC Cardiovasc Disord 2020;20:201. PUBMED | CROSSREF
3. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J 2015;36:1012-1022. PUBMED | CROSSREF
4. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA; The National Lipid Association's Muscle Safety Expert Panel. An assessment by the statin muscle safety task force; 2014 Update. J Clin Lipidol 2014;8:S58-S71. PUBMED | CROSSREF
5. Warden BA, Guyton JR, Kovacs AC, Durham JA, Jones LK, Dixon DL, et al. Assessment and management of statin-associated muscle symptoms (SAMS): A clinical perspective from the National Lipid Association. J Clin Lipidol 2023;17:19-39. PUBMED | CROSSREF
6. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. J Am Coll Cardiol 2016;67:2395-2410. PUBMED | CROSSREF
7. Sibley RA, Katz A, Papadopoulos J. The interaction between rosuvastatin and ticagrelor leading to rhabdomyolysis: a case report and narrative review. Hosp Pharm 2021;56:537-542. PUBMED | CROSSREF
8. van Vuren AJ, de Jong B, Bootsma HP, Van der Veen MJ, Feith GW. Ticagrelor-induced renal failure leading to statin-induced rhabdomyolysis. Neth J Med 2015;73:136-138. PUBMED
9. Sirvent P, Mercier J, Lacampagne A. New insights into mechanisms of statin-associated myotoxicity. Curr Opin Pharmacol 2008;8:333-338. PUBMED | CROSSREF
10. Meda C, Plank C, Mykhaylyk O, Schmidt K, Mayer B. Effects of statins on nitric oxide/cGMP signaling in human umbilical vein endothelial cells. Pharmacol Rep 2010;62:100-112. PUBMED | CROSSREF
11. Antons KA, Williams CD, Baker SK, Phillips PS. Clinical perspectives of statin-induced rhabdomyolysis. Am J Med 2006;119:400-409. PUBMED | CROSSREF
12. Kariyanna PT, Haseeb S, Chowdhury YS, et al. Ticagrelor and statin interaction induces rhabdomyolysis and acute renal failure: case reports and scoping review. Am J Med Case Rep. 2019;7:337-341. CROSSREF
13. Vrkić Kirhmajer M, Macolić Šarinić V, Šimičević L, Ladić I, Putarek K, Banfić L, et al. Rosuvastatin-induced rhabdomyolysis - possible role of ticagrelor and patients' pharmacogenetic profile. Basic Clin Pharmacol Toxicol 2018;123:509-518. PUBMED | CROSSREF
14. Danielak D, Karaźniewicz-Łada M, Główka F. Assessment of the risk of rhabdomyolysis and myopathy during concomitant treatment with ticagrelor and statins. Drugs 2018;78:1105-1112. PUBMED | CROSSREF
15. Martín Navarro JA, Gutiérrez Sánchez MJ, Petkov Stoyanov V, Jiménez Herrero MC. Acute renal failure secondary to rhabdomyolysis in a patient receiving treatment with ticagrelor and atorvastatin. Nefrologia (Engl Ed) 2019;39:448-450. PUBMED | CROSSREF
16. Mendes P, Robles PG, Mathur S. Statin-induced rhabdomyolysis: a comprehensive review of case reports. Physiother Can 2014;66:124-132. PUBMED | CROSSREF
17. Cheeley MK, Saseen JJ, Agarwala A, Ravilla S, Ciffone N, Jacobson TA, et al. NLA scientific statement on statin intolerance: a new definition and key considerations for ASCVD risk reduction in the statin intolerant patient. J Clin Lipidol 2022;16:361-375. PUBMED | CROSSREF
18. Liao JK. Safety and efficacy of statins in Asians. Am J Cardiol 2007;99:410-414. PUBMED | CROSSREF
19. Lee E, Ryan S, Birmingham B, Zalikowski J, March R, Ambrose H, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 2005;78:330-341. PUBMED | CROSSREF

20. Mahadevan L, Yesudas A, Sajesh PK, Revu S, Kumar P, Santhosh D, et al. Prevalence of genetic variants associated with cardiovascular disease risk and drug response in the Southern Indian population of Kerala. Indian J Hum Genet 2014;20:175-184. PUBMED | CROSSREF

21. Gupta M, Braga MF, Teoh H, Tsigoulis M, Verma S. Statin effects on LDL and HDL cholesterol in South Asian and white populations. J Clin Pharmacol 2009;49:831-837. PUBMED | CROSSREF