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Ticagrelor and Statin Interaction Induces Rhabdomyolysis and Acute Renal Failure: Case reports and Scoping Review

Pramod Theetha Kariyanna[1], Syed Haseeb[1], Yuvraj Singh Chowdhury[1], Apoorva Jayarangaiah[2], Andrii Maryniak[1], George Mo[1], Sudhanva Hegde[1], Jonathan D. Marmur[1], Isabel. M. McFarlane[1,*]

[1]Division of Cardiovascular Disease and Department of Internal Medicine, State University of New York: Downstate Medical Center, Brooklyn, New York, United States-11203.
[2]Department of Internal Medicine, NYC Health and Hospitals/Jacobi Medical Center, Bronx, N.Y., U.S.A-10461
*Corresponding author: Isabel.McFarlane@downstate.edu

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Abstract Ever since evidence about the increased risk of stent thrombosis with drug eluting stents (DES) surfaced in 2005, the Food and Drug Administration (FDA) has recommended the use of dual antiplatelet therapy (aspirin with P2Y12 inhibitor) following DES placement. The PLATO trial demonstrated lower mortality rates with the use of Ticagrelor when compared to clopidogrel (9.8% vs. 11.7%, p<0.001) when treating patients with acute coronary syndrome. Given their pleiotropic benefits, statins are today the second most prescribed drug in the United States and often co-prescribed with Ticagrelor. FDA's post market surveillance of Ticagrelor use along with statins in post-myocardial infarction care is now revealing novel and serious adverse events. We present two cases of rhabdomyolysis and acute renal failure (ARF) which develop while the patients were on statins and Ticagrelor. Case 1: A 66-year-old female presented with bilateral thigh pain for 3 days. One month prior to presentation, she was managed for non-ST segment elevation myocardial infarction (NSTEMI) and had been started on aspirin, ticagrelor and simvastatin. Laboratory values revealed creatinine kinase (CK) level at 40,000 U/L and creatinine 3.2 mg/dL suggesting rhabdomyolysis and ARF. Case 2: A 63-year-old male presented with generalized body aches and fatigue for 4 days. He had sustained STEMI two months before and received two drug eluting stents (DES) and aspirin, ticagrelor and rosuvastatin had been initiated. CK was 380,000 U/L and creatinine 7.94 mg/dL suggesting rhabdomyolysis and ARF. Both patients presented with rhabdomyolysis and acute renal failure within weeks after ticagrelor and statin were commenced. A review of the literature indicated that 11 similar cases of ticagrelor-induced ARF and rhabdomyolysis had been reported. Ticagrelor competes with statins when metabolized by cytochrome P450 (CYP) 3A4 leading to statin retention, leading to major adverse effects like rhabdomyolysis and acute renal failure. Our review is intended to alert clinicians about this important drug interaction.

Keywords: *ticagrelor, statins, rhabdomyolysis, acute renal failure, drug interaction, cytochrome P450 (CYP) 3A4, adenosine diphosphate (ADP) receptor P2Y12*

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1. Introduction

Use of dual antiplatelet (DAPT) and lipid lowering agents is the cornerstone in the management of patients with acute coronary syndrome (ACS). The Clopidogrel and Metoprolol in Myocardial Infarction Trial, (COMMIT) [1] and Clopidogrel in Unstable angina to prevent Recurrent Events, (CURE) [2] trials demonstrated reduction in mortality and major vascular events in ACS when the P2Y12 inhibitor clopidogrel was co-administered with aspirin in patients with ACS. The Platelet Inhibition and Patient Outcomes (PLATO) trial [3] trial established lower mortality rates with the use of Ticagrelor when compared to clopidogrel (9.8% vs. 11.7%, p<0.001) when treating patients with ACS. The trial also demonstrated higher platelet reactivity and worse clinical outcomes in patients with diabetes with the use of clopidogrel. Clopidogrel and ticagrelor act on $P2Y_{12}$-receptor as direct antagonists. Ticagrelor however, unlike clopidogrel acts reversibly on this receptor. Ticagrelor is not only faster in onset but is also a more potent inhibitor of platelet aggregation [4]. The Food and Drug Administration's (FDA) post market surveillance of Ticagrelor use along with statins in post-myocardial infarction care is now revealing novel and serious adverse events [5]. We present two cases of rhabdomyolysis and

acute renal failure their use and a scoping review on this interaction.

2. Case Presentation 1

A 66-year-old woman presented with bilateral cramping thigh pain for three days. She had no antecedent history of trauma, infection, severe exercise, seizures, uncontrolled blood glucose or use of herbal medication. She had a history of coronary artery disease, heart failure, diabetes, hypertension, and hyperlipidemia. A month prior, she was admitted to the hospital for a non-ST elevation myocardial infarction (NSTEMI). Invasive strategy versus medical therapy was discussed. Given that she had diffuse disease which was not amenable to percutaneous coronary intervention (PCI), medical management with dual antiplatelet therapy (DAPT) was instituted. Her secondary prevention regimen included Ticagrelor 90 mg twice daily in addition to, her past medications: Aspirin, Nifedipine, Losartan, Simvastatin, Metoprolol and Furosemide 20 mg as needed. At discharge, her serum creatinine (SrCr) concentration was 1.44 mg/dl and serum creatinine-kinase (CK) concentration was 203 U/L.

On presentation, laboratory investigations were significant for a Sr Cr. of 2.93 mg/dL and CK of 22,000 U/L. She was diagnosed with acute on chronic kidney injury (underlying CKD stage II) and acute rhabdomyolysis with CK levels peaking close to ~40,000 U/L by hospital day 2. Urinalysis demonstrated 2+ proteinuria and 3+ hemoglobinuria, with only 3 RBC seen. She was started on aggressive intravenous (IV) hydration and simvastatin and ticagrelor were discontinued. Her symptoms resolved, CK levels promptly decreased [Figure 1] and the Sr Cr. decreased to 2.3 mg/dl. On discharge, she was started on clopidogrel. During a follow up clinic visit, the patient was prescribed rosuvastatin and has remained without complications on follow up visit and laboratory checks.

3. Case Presentation

A 63-year-old male reported generalized muscle pain and weakness for four days. He had no history of trauma, infection or excessive physical exertion. He had a history of coronary artery disease, congestive heart failure, hyperlipidemia, and hypertension. Two months prior, he was admitted to the hospital for an ST-elevation myocardial infarction. He was loaded with Ticagrelor, ASA, and heparin bolus and taken to the cardiac catheterization suite for primary PCI. Angiography revealed triple vessel disease with the mid-right coronary artery (RCA) identified as the culprit lesion. A drug eluting stent was placed in the mid-RCA. Post intervention echocardiogram demonstrated a left ventricular ejection fraction (LVEF) of 40-45% with infero-septal wall hypokinesia. He was discharged on a secondary prevention regimen which included: Ticagrelor, Aspirin, Metoprolol and Rosuvastatin. Referral to cardiothoracic surgery was made for evaluation of coronary artery bypass graft. Prior to discharge, his Sr Cr. concentration was 0.73 mg/dl and serum creatinine-kinase (CK) concentration was 193 U/L.

On presentation, his laboratory results showed a Sr Cr of 7.94 g/dL and CK of 227,108 U/L peaking at ~380,000 U/L by hospital day 5. He had normal thyroid function tests and negative titers for ANA, ds-DNA, anti-Jo, antineutrophilic cytoplasmic antibodies: p-ANCA and c-ANCA. Renal ultrasonography was unremarkable for obstructive uropathy as a cause for the ARF. The patient underwent continuous veno-venous hemodialysis for 6 days. Ticagrelor and simvastatin were discontinued. His kidney function recovered and he was discharged home on rosuvastatin and clopidogrel. No further recurrences were reported on outpatient follow-up visits.

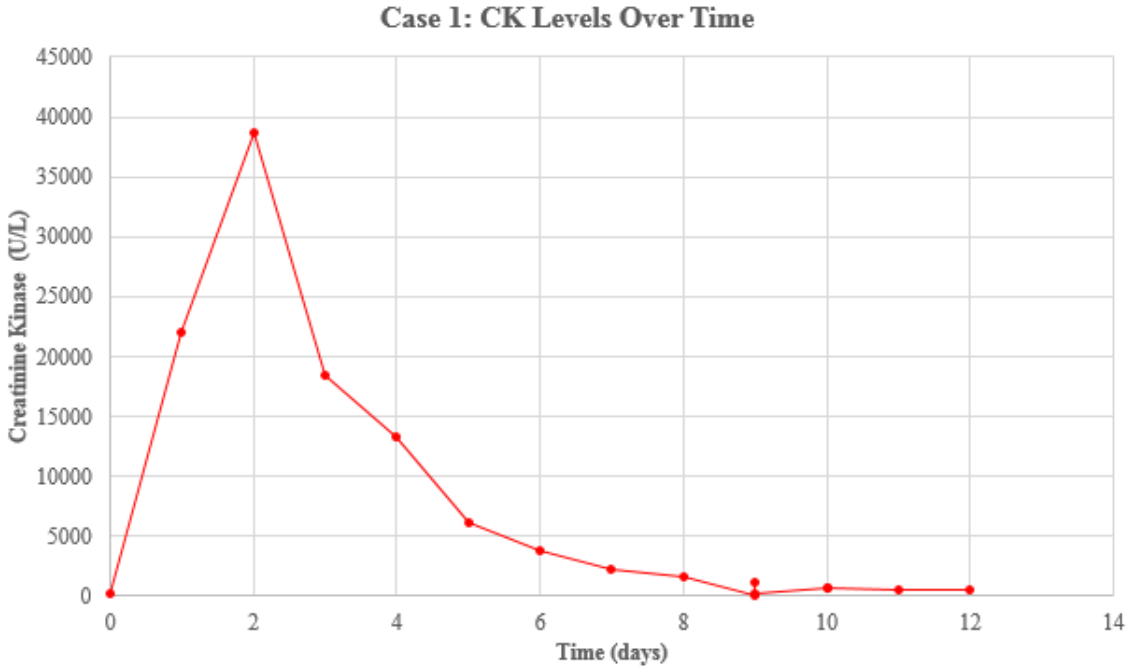

Figure 1. Graph demonstrating Creatinine Kinase values for Case 1

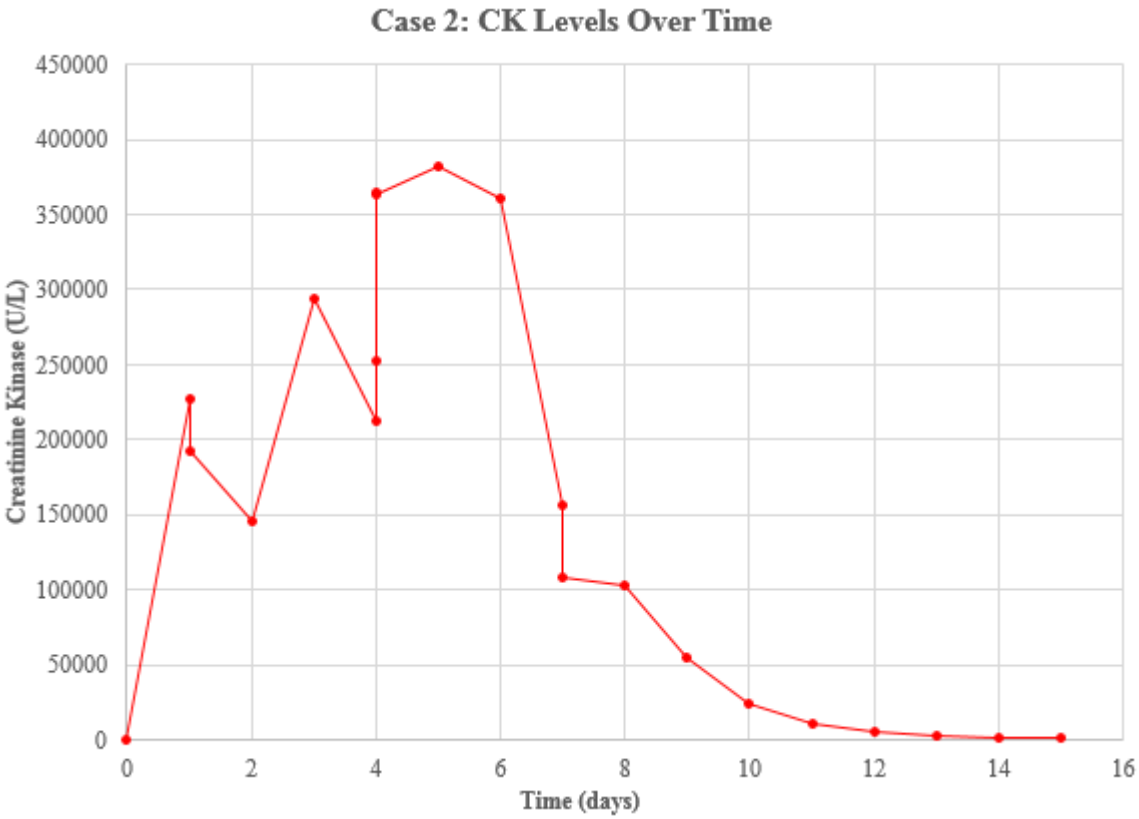

Figure 2. Graph demonstrating Creatinine Kinase values for Case 2

4. Discussion

Rhabdomyolysis is a complex condition characterized by disruption of the integrity of the skeletal muscles resulting in the release of sarcoplasmic proteins such as aspartate aminotransferase, alanine aminotransferase, CK and electrolytes into the circulation. Patients typically present with myalgias and muscle weakness. Rhabdomyolysis can lead to potentially life-threatening complications like ARF, compartment syndrome and cardiac arrhythmias [6].

Rhabdomyolysis and subsequent acute tubular necrosis from toxic effects of myoglobinuria are well-documented adverse effects of statin use [7]. Proposed mechanisms involve either muscle structural instability due to a reduced cholesterol content or inhibition of biosynthetic pathways [8]. Simvastatin accounts for 18.3%, atorvastatin 11.5% and pravastatin accounts for 7.3% cases [9]. The 80 mg dose of simvastatin was recently found to have a 7-fold higher rate of rhabdomyolysis when compared to an intermediate intensity statin and was taken off the list of approved doses of high intensity statins [10]. The risk of this toxicity is greater with concurrent use of drugs that inhibit or are metabolized by the cytochrome p450-3A4 (CYP3A4) pathway. A recent report from the FDA ascribes that close to 50 percent of all rhabdomyolysis cases are due to drug interactions.

Ticagrelor is a reversible oral antagonist of the adenosine diphosphate (ADP) receptor P2Y12. It is rapidly absorbed and metabolized by cytochrome P450 (CYP) 3A4. Ticagrelor and statins are often co-prescribed, especially among post-myocardial infarction patient population, and both drugs are metabolized by the same cytochrome P450 (CYP) 3A4. Ticagrelor acts as a competing substrate for the enzyme and delays the metabolism of statins leading to its accumulation [11]. In addition, due to the same competing metabolism in the liver, some of the hydrophilic statins are retained during acute kidney insufficiency. Ticagrelor is also known to increase serum creatinine levels by 30%. Ticagrelor induced-renal insufficiency can also result in statin retention and may potentiate the risk of statin-induced myopathy which may in turn further worsen the acute renal failure. Both of these postulated mechanisms can explain statin toxicity in relation to ticagrelor use [12]. An FDA review has demonstrated high renal dysfunction in ticagrelor-treated patients who were concomitantly treated with angiotensin receptor blockers (ARB) compared to ticagrelor-treated patients who did not receive ARBs [12]. Angiotensin converting enzyme (ACE) inhibitors and ARBs are drugs commonly prescribed to the same patient population receiving statins and Ticagrelor which might further contribute to ARF and thus statin retention and toxicity [13].

Our patients presented with rhabdomyolysis and ARF within weeks after being prescribed both, ticagrelor and statins. Drug interaction, was suspected given the elevated CK and SRCr values in the absence of another triggering event. The medications were held and patients were provided appropriate resuscitation. Once the AKI and rhabdomyolysis resolved, the P2Y12 inhibitor for both patients was switched to Clopidogrel. At two month-follow up, both patients denied recurrence of the symptoms and the laboratory data remained without evidence of CK elevation.

A review of literature revealed eleven [14-24] reported cases of ticagrelor induced ARF and rhabdomyolysis (Table 1). 10 cases were found in patients who were also on prescription of high intensity statins with rosuvastatin

being the most commonly used statin. Nine cases had concomitant use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). These cases highlight that the adverse interaction, between ticagrelor and statins leading to rhabdomyolysis and potentially acute renal failure, might be more common than considered in clinical practice.

Table 1. Reported Cases Ticagrelor-Induced Acute Renal Failure and Rhabdomyolysis [14-24]

Cases	11	
Sex (n=10)	Men 4 & Women 6	
Age in years ± SD	Mean 70.55 ± 10.66 Median 72	
Chief complaint	Generalized weakness Myalgia Nausea/vomiting Prox. muscle weakness Syncope Decreased urine output Decrease oral intake Red urine	5 4 4 3 1 1 1 1
Statin used	Rosuvastatin Atorvastatin Simvastatin High intensity statin dosage used	7 3 1 10
Other medications that possibly contributed to	Concomitant used of ACEi/ARB Amlodipine Proton pump inhibitors NSAIDs	9 3 3 1
Average time	50 ± 17.6 days	

ACEi angiotensin-converting-enzyme inhibitor, **ARB** angiotensin II-receptor blocker
NSAIDs non-steroidal anti-inflammatory drugs.

Large scale survey-based studies such as Prediction of Muscular Risk in Observational Conditions (PRIMO) and Understanding Statin Use in America and Gaps in Patient Education (USAGE), as well as large randomized controlled trials such as The Effect of Statin Medications on Muscle Function and Performance (STOMP), have unequivocally identified a significant prevalence of myopathy in patients on statin therapy [25,26,27]. Which statins are more frequently implicated and why is of particular interest. The difference in prevalence of statin-induced myopathy between classes lies in their pharmacokinetics and lipophilicity. Because lipophilic statins such as simvastatin, and atorvastatin have the ability to non-selectively diffuse into extrahepatic tissues such as skeletal muscle, they are associated with the highest risk of myopathy. In contrast, hydrophilic statins such as pravastatin and rosuvastatin are hepatoselective, requiring OTAP-mediated active transport into hepatocytes, and thus accumulate less in skeletal muscle [28,29]. Other factors such as genetic predisposition in patients with *SLCO1B1* genotypes, and concomitant use of drugs which competitively inhibit specific cytochrome P450 isoforms, required for statin metabolism and excretion, are less clear in explaining differences in prevalence of statin-induced myopathy among different classes [28,30].

Evidence supporting the secondary preventative benefit of statins has compelled several authorities such as the American Heart Association, the Canadian Consensus Working Group, and the European Atherosclerosis Society to establish clear guidelines and strategies to re-challenge patients with previous statin-induced myopathy and elevations in creatine kinase. Temporary cessation of statin therapy for up to 2 months depending on the level of CK elevation and degree of muscle weakness, and identification of symptomatic and biochemical improvement is necessary to establish causation. Subsequent intervention includes titration of statin therapy to identify the maximally tolerated dose, replacement of lipophilic statins with hydrophilic statins, combination therapy with the maximally tolerated dose of statin plus another lipid-lowering agent, and least favorably, exclusive treatment with other anti-hyperlipidemic medications when statins cannot be tolerated altogether [25,31,32,33]. This stepwise approach is generally accepted when treatment of hyperlipidemia is necessary for secondary prevention; other considerations apply to patients for whom statins are prescribed as primary prevention. Other approaches include correction of vitamin D deficiency and hypothyroidism, in order to reduce the risk of repeat myopathy, and introduction of PCSK9 inhibitors which may benefit patients with high ASCVD but are statin-intolerant [31,34].

5. Conclusion

Ticagrelor competitively inhibits statin metabolism with cytochrome P450. Ticagrelor also independently causes renal insufficiency. The combination of these can result in statin retention and increased levels may lead to rhabdomyolysis and ARF. ACEI/ARBs commonly used in patients with hypertension, heart failure and ACS/CAD can increase Sr Cr. by inducing efferent arteriolar vasodilation leading to elevated blood levels of statins. Physicians should be aware that the utilization of these two drugs can lead to rhabdomyolysis and ARF due to a competition of the cytochrome p450-3A4 (CYP3A4) pathway.

Acknowledgments

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