

# Rhabdomyolysis precipitated by possible interaction of ticagrelor with high-dose atorvastatin

Kazuhiko Kido, Mary B. Wheeler, Arash Seratnahaei, Alison Bailey, and Jonathan A. Bain

## Abstract

**Objective:** To report a case of rhabdomyolysis possibly caused by interaction of ticagrelor with high-dose atorvastatin.

**Summary:** A 62-year-old woman originally from India underwent uncomplicated percutaneous coronary intervention following ST-elevation myocardial infarction. The patient was discharged on a secondary prevention drug regimen that included ticagrelor 90 mg twice daily, atorvastatin 80 mg once daily, metoprolol 25 mg twice daily, and aspirin 81 mg daily. Two months later, the patient was readmitted with complaints of muscle pain, nausea, vomiting, and poor oral intake. The patient was diagnosed with rhabdomyolysis based on her symptoms combined with elevated creatine kinase, urine myoglobin, and serum creatinine. Intravenous fluids were initiated and atorvastatin held. Throughout the second hospital stay, serial laboratory values revealed a decrease in creatine kinase and resolution of acute kidney injury and muscle pain. The patient was discharged on aspirin and clopidogrel. Low-dose statin therapy was started at a follow-up appointment with close monitoring without recurrence of rhabdomyolysis.

**Results:** A drug interaction between the cytochrome P450 3A4 inhibitor ticagrelor and substrate atorvastatin 80 mg may have precipitated development of rhabdomyolysis in this patient. The probability of this drug interaction is rated as "possible" on both the Naranjo Adverse Drug Reaction Probability Scale and the Drug Interaction Probability Scale.

**Conclusion:** Rhabdomyolysis was observed possibly because of a drug interaction between once-daily ticagrelor and atorvastatin 80 mg. Clinicians need to be aware of this possible drug interaction via CYP3A4 and potential complications.

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Statins, or 3-hydroxy-3-methylglutaryl coA reductase inhibitors, are prescribed primarily in cardiovascular disease for their effect on reducing the synthesis of mevalonate, which acts as a critical step within the cholesterol pathway.<sup>1,2</sup> High-dose statin therapy is recommended after acute coronary syndrome (ACS). Specifically, atorvastatin 80 mg was shown to have superior efficacy to pravastatin 40 mg for the composite cardiovascular outcome of death, myocardial infarction, or rehospitalization for recurrent ACS at 30 days.<sup>3</sup>

Myopathies associated with statin are prevalent and have been reported for years. The Adverse Event Reporting System database of the Food and Drug Administration contains more than 600 reported cases of rhabdomyolysis associated with statin use between November 1997 to March 2000.<sup>4</sup> While the number of reported rhabdomyolysis cases is high, the clinical impact for rhabdomyolysis remains unclear, as there is a low reported mortality rate of 0.15 deaths per 1 million prescriptions.<sup>5</sup>

The exact mechanism whereby statins cause muscle injury is not well understood. One theory regarding the etiology of statin myopathy is that by blocking cholesterol synthesis, the cholesterol content of the skeletal muscle cell membrane is decreased, which makes the cells unstable. This theory is supported by similar observations with clofibrate and niacin, which also cause muscle injury.<sup>6-8</sup>

We report here the first published case of possible rhabdomyolysis associated with drug interaction between ticagrelor and atorvastatin 80 mg and review publications to support this drug interaction.

### Case report

A 62-year-old woman originally from India (weight, 73 kg; body mass index, 45.7 kg/m<sup>2</sup>) was admitted with acute ST-elevation myocardial infarction. Before

catheterization the patient received a loading dose of ticagrelor 180 mg with aspirin 324 mg. The coronary angiogram revealed acute plaque rupture in the right coronary artery. A 3.0 mm x 23 mm everolimus-eluting stent was placed.

During the hospital stay, a standard-of-care secondary prevention medical regimen was initiated with ticagrelor 90 mg twice daily, atorvastatin 80 mg once daily in the evening, metoprolol tartrate 25 mg twice daily, and aspirin 81 mg once daily. The patient displayed no evidence of ischemic heart failure, and a postintervention transthoracic echocardiogram revealed an ejection fraction of 65%. Her serum creatinine was 0.73 mg/dL and her other laboratory values were unremarkable during hospitalization. The patient was discharged on the secondary preventive regimen.

Two months later, the patient presented to the emergency department with complaints of muscle pain, nausea, vomiting, and poor oral intake for the prior 48 hours. She reported one episode of emesis, describing a clear, nonbilious liquid, and stated that her discomfort was dissimilar from pain experienced during her myocardial infarction. She reported adherence with her medication regimen since discharge.

Initial laboratory tests revealed several abnormalities including hyponatremia; elevated serum creatinine, liver enzymes, and creatine kinase (CK); minimally elevated troponin; and urine myoglobin of 72,434 ng/mL (Table 1).

**Table 1.** Laboratory values during hospitalization for rhabdomyolysis

Laboratory tests	On admission	At discharge (day 9)
Urine myoglobin (ng/mL)	72,434	N.A.
Urea nitrogen, blood (mg/dL)	30	12
Serum creatinine (mg/dL)	2.91	0.78
Sodium (mmol/L)	121	137
Potassium (mmol/L)	3.7	3.9
Chloride (mmol/L)	87	111
Troponin (ng/mL)	0.07	N.A.
Aspartate aminotransferase (U/L)	498	425
Alanine aminotransferase (U/L)	364	372
Alkaline phosphatase (U/L)	412	425
Bilirubin, total (mg/dL)	2.1	1.6
Creatine kinase (U/L)	5270	4484
Glomerular filtration rate (mL/min/1.73m <sup>2</sup> )	16	>60
Abbreviation used: N.A., not available.		

### Key Points

#### Background:

- Dual antiplatelet (including P2Y12 inhibitors) and high-dose statins are frequently used in combination after myocardial infarction.
- Ticagrelor plus high-dose atorvastatin is a previously known possible drug interaction.

#### Findings:

- We report the first known case of suspected drug interaction resulting in rhabdomyolysis from ticagrelor plus high-dose atorvastatin.
- This case increases awareness of rhabdomyolysis as a complication of ticagrelor and high-dose atorvastatin use.

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