Myopathy and Rhabdomyolysis with Concomitant Use of Ticagrelor and High-Intensity Statins

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BACKGROUND

- The American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines recommend that in ACS (Acute Coronary Syndrome) patients treated with dual antiplatelet therapy after coronary stent implantation and in patients with NSTE-ACS treated with medical therapy alone, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y12 inhibitor therapy.[1]
- In very high-risk ASCVD (atherosclerotic cardiovascular disease), the use of high-intensity statins (i.e., atorvastatin 40 or 80 mg; rosuvastatin 20 or 40 mg) is advised in secondary prevention.[2]
- Atorvastatin is metabolized by CYP3A4, while rosuvastatin metabolism is not dependent on CYP3A4 to a clinically significant extent.
- In patients >75 years of age with clinical ASCVD, it is reasonable to initiate moderate (i.e., atorvastatin 10 or 20 mg; rosuvastatin 5 or 10 mg) or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preferences.[2]
- Despite the advantages of concomitant use of ticagrelor and statins, reports of myopathy and rhabdomyolysis were received in the postmarket setting.

OBJECTIVES

- To characterize postmarketing adverse event reports of myopathy and rhabdomyolysis associated with concomitant use of ticagrelor and atorvastatin or rosuvastatin, submitted to the US Food and Drug Administration Adverse Event Reporting System (FAERS)
- To assess the concomitant use of ticagrelor and atorvastatin or rosuvastatin in the Sentinel Distributed Database (SDD). (https://www.sentinelinitiative.org)

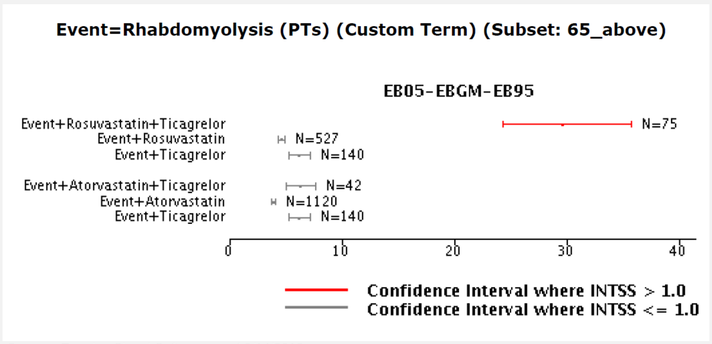
METHODS

- We used the Empirica Signal software to analyze disproportionality of reporting of rhabdomyolysis (custom term) associated with the concomitant use of ticagrelor and atorvastatin or rosuvastatin '3-dimensional analysis' (3D) in the FAERS data from January 2012 to September 2018 using the Bayesian datamining interaction signal score (INTSS).[3]
- We queried FAERS for reports of myopathy/rhabdomyolysis associated with concomitant use of ticagrelor and atorvastatin or rosuvastatin from US approval of ticagrelor to September 2018. Reports were included if both drugs were initiated at the same time or the patient was on a statin prior to ticagrelor initiation. We assessed causality using the Drug Interaction Probability Scale (DIPS).[4]
- We used the SDD to identify prevalent concomitant dispensings of ticagrelor and atorvastatin or rosuvastatin using National Drug Codes (NDC) from January 2012 to June 2018. Dispensings of ticagrelor were evaluated for concomitancy of atorvastatin or rosuvastatin in a window 30 days prior to 60 days post dispensing. Dispensings were evaluated by each atorvastatin or rosuvastatin strength.

RESULTS

- The 3D datamining analyses of ticagrelor with rosuvastatin produced an INTSS >1.0, which was driven by disproportionate reporting in those ≥ 65 years of age. The combination of ticagrelor and atorvastatin produced an INTSS < 1.0 across all reports using crude counts.(**Figure 1**)
- We identified 45 cases of myopathy (n=7) and rhabdomyolysis (n=38) with concomitant use of ticagrelor and atorvastatin (n=24) or rosuvastatin (n=21), including death cases (n=3). Approximately 50% of the reported cases occurred in patients ≥75 years. (**Table 1**).

Figure 1. 3D Data Mining Results ≥65 years



Source : Empirica Signal Software as of 9/14/2018

RESULTS (Cont'd.)

Table 1. Characteristics of Ticagrelor FAERS Cases Concomitant with Atorvastatin or Rosuvastatin Associated with Myopathy/Rhabdomyolysis *

Selected Characteristics (n=45)	Atorvastatin started before ticagrelor initiation (n=8)	Atorvastatin started at the same time as ticagrelor (n=16)	Rosuvastatin started before ticagrelor initiation (n=6)	Rosuvastatin started at the same time as ticagrelor (n=15)
Age (years)				
Range	57-79	44-89	46-85	49-89
0-64	3	3	1	6
≥65	2	6	3	1
≥75	3	7	2	8
Sex				
Female	4	9	3	10
Male	4	7	3	5
Time-to-onset (days) Median (range)	60 (1-90)	34 (2-330)	47 (30-548)	45 (14-255)
Ticagrelor dose				
90 mg BID	8	16	6	15
Atorvastatin/Rosuvastatin Strength (mg)§				
Ator 20/Rosu 10	-	1	-	5
Ator 40/Rosu 20	1	3	2	3
Ator 80/Rosu 40	7	11	3	5
Not reported	-	1	1	2
Spectrum of statin-induced myopathy				
Rhabdomyolysis	6	15	6	11
Asymptomatic CK elevation	1	-	-	-
Myopathy/Myalgia	1	1	-	4
Creatinine kinase levels (U/L)				
Median (range)	14,300 (2,360 -100,000)	27,745 (5,270 - 58,000)	10,872 (1,300 - 28,167)	15,789 (342 - 338,601)
Not reported	2	5	1	5
Clinical Outcome¥				
Acute Kidney Injury	5	9	3	9
Dialysis	1	2	1	3
Not reported	2	5	2	6
Dechallenge€				
Statin discontinued	7	13	5	13
Ticagrelor discontinued	4	5	2	7
Not reported	1	7	3	3
Risk Factors ¥				
Baseline renal impairment	2	-	1	7
CYP3A4 Inhibitor	2	4	-	-
CYP2C9/OAT1B1 Inhibitor	-	-	1	3
Polypharmacy¶	4	8	2	8
DIPS§ Causality				
Probable	3	-	-	-
Possible	5	16	6	15

*As of September 11, 2018

¥More than one or no clinical risk factors or outcome may have been reported per case

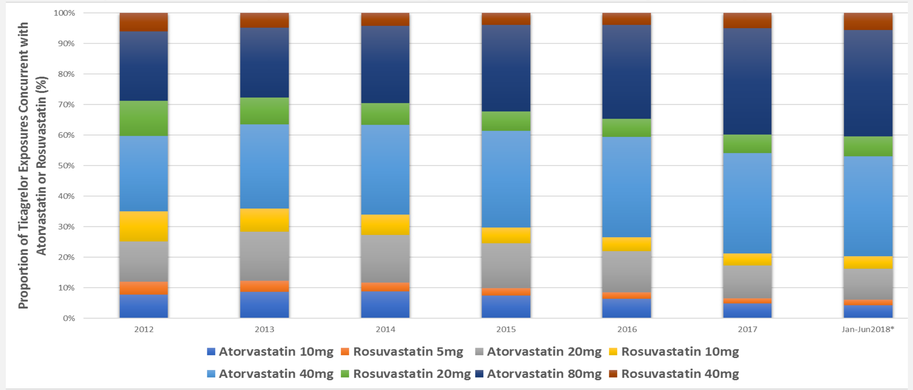
€Cases may have reported statin or ticagrelor discontinuation or both

¶Polypharmacy defined as ≥ five medications

§Statin doses presented by ACC/AHA classification intensity[5]. No cases were reported with Atorvastatin 10mg or Rosuvastatin 5mg

- Drug utilization data obtained from SDD (**Figure 2 and Figure 3**) showed the following:
  - Out of all ticagrelor exposures concomitant with atorvastatin or rosuvastatin among all ages, proportions of ticagrelor exposures concurrent with high-intensity statins increased from 65% of total concurrent exposures in 2012 to 73% in 2016 (**Figure 2**)
  - Out of all ticagrelor 90mg exposures in patients ≥75 years, the proportion of concomitant use with high-intensity statins increased from 57% in 2012 to 66% in 2016 **(Figure 3)**

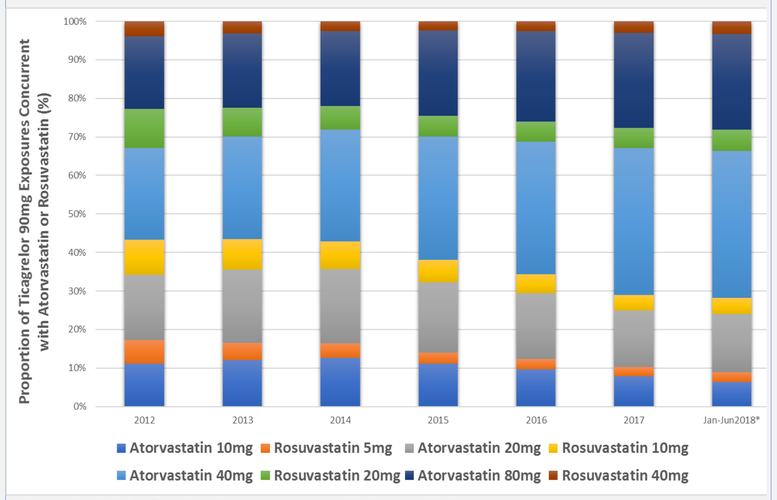
Figure 2. Proportion of Ticagrelor Exposures with Concomitant Atorvastatin or Rosuvastatin Exposure, Stratified by HMG CoA reductase Inhibitor and Product Strength, among the 100% Medicare Fee-for-Service Population and a Sample of Commercially-Insured Patients of all ages, January 2012-June 2018



Source: Sentinel Distributed Database Years January 2012- June 2018.

RESULTS (Cont'd.)

Figure 3. Proportion of Ticagrelor 90mg Exposures with Concomitant Atorvastatin or Rosuvastatin Exposure in Patients Aged 75 Years and Older, Stratified By HMG CoA Reductase Inhibitor and Product Strength, among the 100% Medicare Fee-for-Service Population and a Sample of Commercially-Insured Patients, January 2012-June 2018



Source: Sentinel Distributed Database. Years January 2012 – June 2018

DISCUSSION & CONCLUSIONS

- Ticagrelor is a known weak inhibitor of CYP3A4 enzyme and P-glycoprotein. An in vivo Pharmacokinetic (PK) study in healthy volunteers (mean age 32 years) showed that ticagrelor increases the serum concentration (AUC) of atorvastatin (CYP3A4 substrate) by 1.4-fold. It's unknown if any PK studies were conducted for the co-administration of ticagrelor and rosuvastatin.[6]
- Despite the use of CYP3A4-metabolized statins in 90% of participants in the Platelet Inhibition and Patient Outcomes (PLATO) trial (with atorvastatin ~40% and rosuvastatin ~9%), the data cannot be used to assess the potentially clinically-significant interactions between ticagrelor and atorvastatin or rosuvastatin because information on the dose of the statin used in patients receiving ticagrelor was not routinely collected in the PLATO trial.[7]
- We identified cases of myopathy and rhabdomyolysis after the initiation of ticagrelor in patients ≥75 years on high-intensity statins. Concomitant use of these drugs increased since 2012. Clinicians should weigh the ASCVD benefits of this combination against this possible risk, especially in patients ≥75 years.

DATABASE LIMITATIONS

Empirica Signal:
- Data mining scores do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation.

FAERS:
- Variable quality of information provided to FDA, reporting bias and under reporting.
- All events and exposures are not captured, so incident rates cannot be calculated.

SDD:
- Results from the 100% Medicare fee-for-service population was captured 2012 through 2016; therefore, patients aged 65 and older may be underrepresented in results for 2017 and 2018.
- The statin doses were determined by using the NDC strength and may not always represent the actual doses taken by patients.

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FINANCIAL DISCLOSURES: The authors of this poster declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this poster, including grants, employment, gifts, stock holdings, and honoraria.

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ACKNOWLEDGMENT: Many thanks are due to Data Partners who provided Sentinel data used in the analysis.