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REVIEW ARTICLE

Assessment of the Risk of Rhabdomyolysis and Myopathy During Concomitant Treatment with Ticagrelor and Statins

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Abstract

The introduction of ticagrelor, one of the first directly-acting oral antiplatelet drugs, provided new possibilities in the prevention of thrombotic events in patients with acute coronary syndromes (ACS). Current guidelines recommend ticagrelor in dual antiplatelet therapy with aspirin over clopidogrel for prevention of stent thrombosis in patients with ACS. Moreover, in the management of ACS, lipid-lowering treatment with high-intensity statin therapy is advised for secondary prevention of cardiovascular events over the long term. Despite the apparent advantages of combined antiplatelet and lipid-lowering treatments, a possible interaction between statins and ticagrelor may lead to myopathy and rhabdomyolysis. In this review, relevant information was gathered on the ticagrelor-statin interaction that might lead to this life-threatening condition. This review focuses on the most widely used statins—simvastatin, atorvastatin, and rosuvastatin. Possible mechanisms of this interaction are discussed, including CYP3A4 isoenzymes, organic anion transporter polypeptide (OATPs), P-glycoprotein and glucuronidation. PubMed database was searched for relevant case reports and all data gathered from the introduction of ticagrelor to March 2018 are presented and discussed. In summary, co-administration of statins and ticagrelor was found to be relatively safe in routinely prescribed doses. However, caution should be exercised, especially in elder populations.

Key Points

The increasing use of ticagrelor for prevention of ischemic events in patients with acute coronary events raises the potential risk of adverse events caused by interactions with statins, leading to rhabdomyolysis.

This interaction might be the result of CYP3A4 inhibition, but other pathways, such as competitive interaction with OATPs or P-glycoprotein, might be involved as well.

Co-administration of statins and ticagrelor was found to be relatively safe in routinely prescribed doses. However, caution should be exercised, especially in elderly populations.

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1 Introduction

Introduction of ticagrelor, of the first directly-acting oral antiplatelet drugs, has provided some new possibilities in the prevention of thrombotic events in patients with acute coronary syndromes (ACS). As a competitive and reversible inhibitor of $P2Y_{12}$, it has a rapid onset of action [1]. Contrary to thienopyridine derivatives, such as clopidogrel or prasugrel, metabolic activation is not required for ticagrelor. Therefore, its action is more predictable and consistent in contrast to the older generation of antiplatelet drugs. Current guidelines of the European Cardiac Society and European Association of Cardio-Thoracic surgery (ECS/EACTS) recommend ticagrelor in a dual antiplatelet therapy with aspirin over clopidogrel for prevention of stent thrombosis in patients with acute coronary syndromes (ACS), regardless of the initial treatment strategy [2]. Similarly, guidelines of the American College of Cardiology and American Heart Association (ACC/AHA) suggest that in patients with non-ST-segment elevation (NSTE-ACS) or ST-segment elevation myocardial infarction (STEMI) who are managed with medical therapy alone, use of ticagrelor in addition to aspirin is more reasonable than clopidogrel [3]. Moreover, in the management of ACS, lipid-lowering

treatment with high-intensity statin therapy is advised for secondary prevention of cardiovascular events over the long term [4]. In patients who were receiving low- or moderate-intensity statin therapy, the intensity of the treatment should be increased. Despite the obvious advantages of combined antiplatelet and lipid-lowering treatments, a possible interaction between statins and ticagrelor may lead to myopathy and rhabdomyolysis. This review aimed to provide comprehensive and up-to-date information on the ticagrelor-statin interaction, including possible mechanisms, pharmacokinetic and pharmacodynamic efficacy as well as data gathered from published case studies. This report focuses on the most widely used statins—simvastatin, atorvastatin, and rosuvastatin. We based the review on a PubMed database search, starting from the introduction of ticagrelor to March 2018. Combinations of the following keywords were used for screening for relevant case studies: "ticagrelor", "AZD6140", "statins", "simvastatin", "atorvastatin", "rosuvastatin", "rhabdomyolysis", "myopathy", "kidney failure", "renal function".

2 Statin-Induced Myopathy and Rhabdomyolysis

Statin-induced myopathy (SIM) or overall muscle-related symptoms during therapy with statins is one of the most frequent adverse events arising from treatment with these drugs. According to various reports, it might affect 10–25% of all patients treated with statins [5]. These symptoms include myopathy, myalgia, myonecrosis, and rhabdomyolysis. The latter is one of the most severe adverse events and requires hospitalization. It is diagnosed most often as an elevation in creatine kinase of more than tenfold over the upper limit of normal with evidence of renal impairment, muscle symptoms, and no other causes of muscle injury [6]. Rhabdomyolysis might occur in 0.1% of subjects treated with statins [7]. Also, the prevalence of this adverse event varies between statins. For example, the incidence of rhabdomyolysis expressed as a rate per 10,000 person-years is lower for atorvastatin and simvastatin (0.6) than for rosuvastatin (1.2) [8]. To date, identifying exact mechanisms underlying SIM has been difficult, but some of following aspects might be associated with this condition: mitochondrial dysfunction, variation in the pharmacokinetics of statins, altered balance in cell degradation and repair, vitamin D deficiency, and reduced production of coenzyme Q10 [9]. Interestingly, it has been shown that lactone metabolites of atorvastatin and 4-hydroxy-atorvastatin have higher concentrations in patients with SIM, 2.4-fold and 3.1-fold, respectively [10].

3 Influence of Ticagrelor on Renal Function

Reports from the PLATO trial showed that in comparison to clopidogrel, an older generation antiplatelet drug, ticagrelor was associated with a significantly higher increase in creatinine concentration at 1 and 12 months of treatment [11]. Of note, the elevation reported in the trial was of little clinical relevance and decreased after cessation of the treatment. Another study based on the results of the PLATO trial showed that levels of cystatin C, a renal function biomarker completely dependent on glomerular filtration rate, were also higher in ticagrelor-treated patients compared with those treated with clopidogrel [12]. However, in patients with chronic kidney disease, ticagrelor was shown to have greater efficacy in reducing mortality with a similar safety profile compared with clopidogrel [13]. Moreover, patients with impaired renal function appear to benefit more (0.77 hazard ratio of the primary endpoint, within a 0.65–0.90 confidence interval) from treatment with ticagrelor as compared with clopidogrel than individuals with normal renal function (0.90 hazard ratio, 0.79–1.02 confidence interval). Also, even though some pharmacokinetic differences have been reported between patients with normal and severe renal impairment (lower maximal concentration and exposure to ticagrelor and higher concentration and exposure to its active metabolite), no dose adjustment for this specific group has been advised [14].

4 Underlying Mechanism of the Ticagrelor–Statin Interaction

4.1 Pharmacokinetic Interaction

To date, pharmacokinetic interaction studies between ticagrelor, atorvastatin, and simvastatin have been performed in healthy volunteers [15]. In this study, 90 mg ticagrelor twice daily was co-administered with a high dose (80 mg) of either atorvastatin or simvastatin. Pharmacokinetic parameters of ticagrelor and its active metabolite were seemingly unaffected by statin co-administration. However, the exposure to both statins was significantly increased. For atorvastatin, and its metabolites—atorvastatin lactone, 2-hydroxy-atorvastatin and 4-hydroxy-atorvastatin—the exposure increased by 36, 32, 33, and 67%, respectively. At the same time, no impact on elimination half-life was noted. More pronounced differences were observed for simvastatin. Exposure to simvastatin and its active metabolite—simvastatin acid—increased by 56 and 52%, respectively. The main conclusion from this study was that simvastatin doses of 40 mg daily or higher should be avoided during antiplatelet therapy with ticagrelor. Simultaneously, an increase in the exposure to atorvastatin is tolerable given the favorable safety profile of this drug

[15]. However, to the authors' knowledge, no comparative pharmacokinetic study was performed for ticagrelor and rosuvastatin. Therefore, the extent of the pharmacokinetic interaction between these two drugs, if any, is unknown.

4.2 CYP-450-Mediated Metabolism

CYP3A4 and CYP3A5 are major isoenzymes involved in phase I metabolism of xenobiotics. They are most abundant as cytochrome P-450 enzymes, accounting for approximately 30% in the liver and 80% in the small intestinal mucosa [16]. According to the results from in vitro studies, ticagrelor is mainly metabolized by CYP3A4 and CYP3A5 isoenzymes [17]. Two major metabolites formed through this pathway are AR-C124910XX and AR-C133913XX [18]. Exposure to AR-C124910XX might reach up to 40% of total exposure to the parent drug. Moreover, AR-C124910XX also exerts an antiplatelet effect through interaction with the $P2Y_{12}$ receptor [19]. Besides inhibition of CYP3A4/5 isoenzymes, it was shown that ticagrelor has moderate CYP2C9-inhibiting properties in vitro.

Among the statins, simvastatin and atorvastatin are mainly metabolized by CYP3A4 isoenzyme [20]. Simvastatin is a prodrug with a lactone structure. As a result of a hydrolysis reaction catalyzed by plasma, liver, and intestinal carboxylesterases, the lactone ring is opened, and a hydroxy acid metabolite is formed [21]. This metabolite is responsible for the observed inhibitory activity of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase and lowering of cholesterol levels. Other simvastatin metabolites, such as 3′-hydroxy-simvastatin, 6′-exomethylenesimvastatin, or 3′,5′-dihydrodiolsimvastatin, are formed in reactions catalyzed by CYP3A4 [22]. Contrary to simvastatin, atorvastatin is administered as a calcium salt of the active hydroxyl acid form. In a coenzyme A-dependent reaction or via an acyl glucuronide pathway a lactone entity might be formed from atorvastatin hydroxyl acid [23, 24]. CYP3A4 isoenzymes might further hydroxylate both atorvastatin acid and the lactone form to *ortho* and *para* hydroxymetabolites. Two-hydroxy-atorvastatin and 4-hydroxy-atorvastatin are equally potent to the parent drug in inhibiting HMG-CoA reductase [25]. At the same time, an inactive lactone form and its hydroxymetabolites are linked with the occurrence of statin-induced myopathy [10, 23]. In contrast to the statins mentioned above, rosuvastatin is metabolized only to a minor extent. As the radioactivity studies show, only approximately 10% of the oral dose is recovered in the metabolite form, and the majority of the drug is excreted in the unchanged form [26]. It is assumed that the most potent CYP involved in rosuvastatin metabolism is CYP2C9, and, to a lesser extent, 1A2, 2C19, 2D6, 2E1, and 3A4 [27].

Although CYP3A4/5 is a major enzymatic pathway, it is difficult to point out clinically important genetic polymorphisms that alter the function of this enzyme. Two polymorphisms in the *CYP3A4* region were identified as being potentially associated with the altered pharmacokinetics of ticagrelor rs62471956 and rs56324128 (*CYP3A4*7*) [28]. To our knowledge, no studies so far have evaluated the influence of these alleles regarding either pharmacokinetics or efficacy and safety of statins.

4.3 Transport Mediated by OATPs

Organic anion transporter polypeptides (OATPs) are members of a superfamily of solute carriers, while genes encoding these proteins are labelled *SLCO*, followed by a family number and a subfamily symbol [29]. Family 1 is the best-characterised group of OATPs. In humans, this family includes four transporters: OATP1A2, OATP1B1, OATP1B3, and OATP1C1 [30]. While OATP1A2 is distributed throughout the body, OATP1B1 and OATP1B3 are liver-specific and located in the basolateral membrane of hepatocytes [30, 31]. Expression of OATP1C1 mRNA has been detected in choroid plexus cells and testes.

The exact involvement of OATPs in the metabolism of ticagrelor and its extent are currently unknown. However, the results from a genome-wide association study showed that some single-nucleotide polymorphisms of *SLCO1B1* (specifically rs113681054 and rs4149056 (*SLCO1B1*5*)) might influence the concentrations of ticagrelor and its metabolite [28]. These variants, which are in linkage disequilibrium, might be associated with the deteriorated function of OATP1B1.

According to the literature, three of the transporters listed above are involved in the metabolism of statins—OATP1B1, OATP1B3, and OATP1A2 [32]. The polypeptide of most noticeable impact appears to be OATP1B1, which is involved in the metabolism of all statins. OATP1B3 also seems to affect the metabolism of rosuvastatin [33]. A genome-wide scan showed that the *SLCO1B1*5* allelic variant, which is a result of substitution in c.521T > C, is strongly associated with an increased risk of myopathy in patients receiving simvastatin [34]. Another study compared patients with severe statin-associated myopathy with controls matched for age, gender, statin type, and dose [35]. The results also suggested a substantial role of *SLCO1B1*5* in statin-induced myopathy. Of note, this association was stronger in simvastatin-treated patients than for those subjects who were receiving atorvastatin. However, a new pharmacokinetic study published in 2017 showed that *SLCO1B1*5* is influencing the pharmacokinetics of atorvastatin, leading to higher exposure of both atorvastatin acid and 2-hydroxy-atorvastatin [36]. Reports on the involvement of *SLCO1B1*5* in the safety of rosuvastatin therapy are conflicting. Some authors found no impact of this allele on the rate of myalgia [37], while others evaluated a 3.67-fold higher risk of myotoxicity in carriers of mutant alleles treated with rosuvastatin [38].

4.4 P-Glycoprotein System

P-glycoprotein (P-gp) is a transmembrane protein that acts as an efflux channel, limiting absorption of drugs into enterocytes, and is encoded by the *ABCB1* gene located in chromosome 7 [39]. This ATP-binding protein, also known as multidrug resistance-1 (MDR-1), is known to have many substrates, which have various structural characteristics. Also, many of them may act as inhibitors or inducers of P-gp.

According to the results of a study by Hochman et al. [40], simvastatin, simvastatin acid, and atorvastatin are transported in an insignificant to a moderate degree by P-gp. Also, the affinity of these statins for P-gp was low. However, some studies suggest that simvastatin might affect the pharmacokinetics of other drugs that are substrates of P-gp, such as diltiazem [41] or doxorubicin [42]. In vitro and pharmacokinetic studies also indicate that acidic forms of statins and their lactone metabolites have different affinities and influences on P-gp [43–46]. Moreover, the extent of cholesterol-lowering benefits of simvastatin and atorvastatin may vary between carriers of different *ABCB1* haplotypes [47, 48]. Rosuvastatin, on the other hand, might have a low impact on P-gp. An in vitro study with MDR tumor cells showed that rosuvastatin interacted with P-gp only at high concentrations and had no influence on inhibition of anticancer agent transport in tumor cells [49]. Also, no influence of *ABCB1* haplotypes on the pharmacokinetics of rosuvastatin was reported [50]. However, it cannot be excluded that some clinically relevant interaction between P-gp and rosuvastatin exists since interindividual variability in the pharmacokinetics of this statin was found to be highly dependent on the *ABCB1* haplotype [51].

A pharmacokinetic interaction study showed that coadministration of ticagrelor with digoxin increased concentrations of the latter by 75% and the exposure by almost 30% [52]. These results suggest that ticagrelor is a weak inhibitor of P-gp. Also, in in vitro studies with Caco-2 cells, ticagrelor was modestly transported by P-gp [53]. However, a common *ABCB1 3435C > T* polymorphism did not affect either the rate of ischemia or bleeding events [54]. Therefore, an interaction of ticagrelor with P-gp might be of little relevance.

4.5 Glucuronidation through UDP-Glucuronosyltransferase

Glucuronidation is an essential step in the clearance of many drugs, leading to more water-soluble products that are more easily excreted. In the previously cited genome-wide association study, it was found that a single nucleotide polymorphism (rs61361928) in a gene coding uridine 5′-diphosho-glucuronosyltransferase 2B7 (UGT2B7) affected observed levels of the ticagrelor active metabolite [28]. Thus, this enzyme might be involved in the metabolism of ticagrelor. The same enzyme is also involved in the metabolism of atorvastatin, catalyzing the reaction leading to the formation of two metabolites—acyl glucuronide and ether glucuronide [55]. Although glucuronidation is also observed in the metabolic pathway of simvastatin, different enzymes are involved—UGT1A1 and UGT1A3 [56]. The same UGTs appear to be involved in the formation of rosuvastatin and atorvastatin glucuronide metabolites [57]. Therefore, this particular pathway might be one of the drug–drug interaction causes for atorvastatin only. Moreover, other authors also suggest that since metabolism of statins is undergone mainly through CYP450 enzymes, and the fraction of drug metabolized by UGTs is most probably small, the probability of pharmacokinetic drug–drug interaction for drugs cleared by glucuronidation is anticipated to be low [58].

5 Review of Reported Case Studies with a Possible Ticagrelor-Statin Interaction

In the following sections, detailed case studies are presented, with reference to co-administered drugs that might amplify a ticagrelor-statin interaction (Table 1). All of the cases are briefly summarized in Table 2.

5.1 Ticagrelor and Simvastatin

Even though low doses of simvastatin are considered safe during ticagrelor treatment, a case has been reported of a 72-year-old male patient who had been treated with simvastatin 20 mg daily [59]. Rhabdomyolysis was diagnosed in this patient 5 months after the introduction of ticagrelor 90 mg twice daily. Ticagrelor was introduced after acute coronary syndrome followed by a percutaneous coronary intervention. Other medications included acetylsalicylic acid, ramipril, pantoprazole, and inhalations of tiotropium bromide and beclomethasone with formoterol. Interestingly, before the incident the patient had normal renal function.

5.2 Ticagrelor and Atorvastatin

One of the first reports of a ticagrelor-atorvastatin interaction was given by Kido et al. [60]. A 62-year-old female patient was admitted and diagnosed with rhabdomyolysis after 2 months of treatment with ticagrelor 90 mg twice daily, atorvastatin 80 mg once daily, metoprolol 25 mg twice daily, and aspirin. Aspirin was with-held, and ticagrelor was switched to clopidogrel. After resolution of acute kidney injury and adjacent muscle pain, low-dose statin therapy was started with close monitoring, without recurrence of rhabdomyolysis.

Concomitant administration of other drugs might also elevate the risk of rhabdomyolysis. In a case of a

Table 1 List of drugs interacting with simvastatin, atorvastatin, rosuvastatin, and ticagrelor, with their respective mechanisms, based on the available product information data [68–71]

Interaction through CYP3A4		Other routes
Inhibition	Induction	
Amiodarone[S]	Rifampicin[A,T]	Gemfibrozil[S,R]
Amlodipine[S]	Efavirenz[A]	Warfarin (CYP2C9)[R,T]
Cyclosporin[S,A,R,T]	Phenytoin[S,A,R,T]	Niacin[A]
Clarithromycin[S,A,T]	Carbamazepine[T]	Rifampicin (OATP1B1)[A]
Danazol[S]	Phenobarbital[T]	Fusidic acid[A,R]
Diltiazem[T]	Dexamethasone[T]	Colchicine[A]
Dronedarone[R]		Eltrompobag (CYP450 substrate, UGT glucuronidation)[R]
Erythromycin[S,A,T]		Cyclosporine (P-pg inhibition)
Fluconazole[T]		Digoxin (P-gp substrate)[A,T]
Grapefruit juice[S,A,T]		Clopidogrel (CYP450, P-gp substrate)[R]
Hepatitis C protease inhibitors[S,A]		
HIV protease inhibitors[A,R,T]		
Itraconazole[S,A,R,T]		
Ketoconazole[S,A,T]		
Verapamil[S,T]		
Voriconazole[S]		

S simvastatin, *A* atorvastatin, *R* rosuvastatin, *T* ticagrelor

Table 2 Summary of case studies reporting a possible interaction between ticagrelor and statins

Statin	Dose of statin (mg)	Age (years)	Sex	Co-administered drugs
Simvastatin [59]	20	72	Male	Aspirin, ramipril, pantoprazole, tiotropium bromide, beclomethasone, formoterol
Atorvastatin [60]	80	62	Female	Aspirin, metoprolol
Atorvastatin [61]	80	74	Female	Amlodipine
Atorvastatin [62]	40	72	Male	Aspirin, bisoprolol, enalapril, clarithromycin
Rosuvastatin [64]	40	78	Male	Amlodipine, omeprazole, Perindopril, metoprolol, ezetimibe
Rosuvastatin [65]	20	49	Female	Lisinopril, metformin, metoprolol, pantoprazole

74-year-old female, severe rhabdomyolysis was diagnosed [61]. The patient was treated with amlodipine (5 mg) and atorvastatin (20 mg) for several years before hospital admission. Two and a half months prior she was diagnosed with ST-elevation myocardial infarction. Subsequently, the dose of atorvastatin was elevated to 80 mg, and ticagrelor 90 mg twice daily was introduced. Muscle biopsy revealed extensive myonecrosis. Of note, amlodipine is a weak inhibitor of CYP3A4. Therefore, co-administration of this drug might lead to increased exposure to both atorvastatin and ticagrelor.

Finally, rhabdomyolysis might also have iatrogenic causes. Cenjor Martin et al. [62] present a case of a 72-year-old male who was undergoing treatment with enalapril 10 mg twice daily, bisoprolol 5 mg, aspirin 300 mg, ticagrelor 90 mg twice daily, and atorvastatin 40 mg for 3 months before admission to hospital for reported polymyalgia and malaise. In addition, due to a recent respiratory infection, the patient was also treated with clarithromycin 250 mg twice daily for several days before admission. After initiation of fluid therapy, clarithromycin and atorvastatin were suspended, with the recommendation of reintroducing atorvastatin at lower doses. Of note, macrolides are known to be potent CYP3A4 inhibitors. Therefore the possibility of adverse event occurrence was high.

5.3 Ticagrelor and Rosuvastatin

A combination of rosuvastatin and ticagrelor is regarded as safe, since rosuvastatin is metabolized by CYP2C9, in contrast to ticagrelor, which is a CYP3A4 substrate. However, some cases of rhabdomyolysis resulting from this interaction have been reported. Also, a report based on the World Health Organization's VigiBase search revealed five unique cases of rhabdomyolysis resulting from concomitant treatment with ticagrelor and rosuvastatin up to October 2016 [63].

In a case of a 78-year-old male, rhabdomyolysis was diagnosed with elevated serum creatinine kinase and serum

creatinine [64]. The patient was receiving rosuvastatin 40 mg once daily, ticagrelor 90 mg twice daily, amlodipine 5 mg, omeprazole 20 mg, perindopril 2 mg, metoprolol 25 mg twice daily, and ezetimibe 10 mg. According to available data, addition of ticagrelor 1 month prior to admission to the hospital was the only recent change in medication. Interestingly, the symptoms of rhabdomyolysis were persisting even after discontinuation of rosuvastatin, amlodipine, and perindopril. Only after removal of ticagrelor did the patient start to recover. It is of note that one of the co-administered drugs was amlodipine, a weak inhibitor of CYP3A4.

A possible rosuvastatin-ticagrelor interaction was also reported for a 49-year-old female patient [65]. Beside 90 mg ticagrelor twice daily and rosuvastatin 20 mg, the patient was treated with lisinopril 20 mg, metformin 500 mg, metoprolol 50 mg twice daily, and pantoprazole 40 mg. The patient's condition improved significantly after cessation of ticagrelor and rosuvastatin. However, the author of the case study did not state how long the treatment with rosuvastatin and ticagrelor was. It might be assumed that ticagrelor was introduced after percutaneous coronary intervention, which took place approximately 6 weeks before the occurrence of rhabdomyolysis symptoms. It was not stated what other drugs were introducted after the intervention procedure.

6 Conclusions

The increased utilization of ticagrelor for prevention of ischemic events in patients with acute coronary events raises the risk of adverse events caused by drug–drug interactions. In this review we have gathered all the relevant information on a ticagrelor-statin interaction that might lead to the development of life-threatening rhabdomyolysis.

Statins, which are widely used due to their obvious advantages in reduction of mortality and cardiovascular events, are frequently prescribed to patients with cardiological disorders. The drawback of statin use is the risk of rhabdomyolysis, which might be dose-related, and which also increases with age for some statins [66]. Indeed, most of the cases presented in this article concern patients older than 70 years.

Most importantly, rhabdomyolysis may be a cause of a direct interaction through inhibition of the CYP3A4 isoenzyme, leading to an increase in the concentration of simvastatin, as well as statins and its metabolites. This interaction might be amplified by co-administration of drugs that are strong or moderate inhibitors of CYP3A4. Still, reported case studies of the interaction between rosuvastatin and ticagrelor that lead to rhabdomyolysis suggest that other pathways might be involved as well. These potential routes might include the competitive interaction of OATPs or P-gp. Moreover, genetic polymorphism affecting the function of transporters, such as the *SLCO1B1*5* allele, is associated by many authors with an increased risk of statin-related myopathy. However, some authors suggest that patient age might be a stronger predictor of muscle symptoms than the presence of *SLCO1B1*5* [67]. It also cannot be excluded that other drugs, such as cyclosporine or rifampicin, might affect transporters, especially P-gp, leading to a further increase in statin concentrations in plasma.

Finally, ticagrelor is used currently in patients with acute coronary syndromes who simultaneously receive intensive, high-dose statin treatment. The latter is most probably responsible for the observed muscule-related complications. Therefore, though a theoretical mechanism of this interaction exists, its clinical significance might be limited. As a consequence, routine checking of parameters associated with this adverse event might not be necessary.

In summary, even though co-administration of statins and ticagrelor was found to be relatively safe in routinely prescribed doses, caution should be used, especially in older populations.

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Compliance with Ethical Standards

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Conflict of Interest Dorota Danielak, Marta Karaźniewicz-Łada, and Franciszek Główka declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

References

1. Danielak D, Karaźniewicz-Łada M, Główka F. Ticagrelor in modern cardiology—an up-to-date review of most important aspects of ticagrelor pharmacotherapy. Expert Opin Pharmacother. 2018;19:103–12.
2. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2018;39:213–60.
3. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of

dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2016;68:1082–115.
4. Roffi M, Patrono C, Collet J-P, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:267–315.
5. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. J Am Coll Cardiol. 2016;67:2395–410.
6. Alfirevic A, Neely D, Armitage J, Chinoy H, Cooper RG, Laaksonen R, et al. Phenotype standardization for statin-induced myotoxicity. Clin Pharmacol Ther. 2014;96:470–6.
7. Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. Am Heart J. 2014;168:6–15.
8. Cziraky MJ, Willey VJ, McKenney JM, Kamat SA, Fisher MD, Guyton JR, et al. Risk of hospitalized rhabdomyolysis associated with lipid-lowering drugs in a real-world clinical setting. J Clin Lipidol. 2013;7:102–8.
9. Taylor BA, Thompson PD. Muscle-related side-effects of statins: from mechanisms to evidence-based solutions. Curr Opin Lipidol. 2015;26:221–7.
10. Hermann M, Bogsrud MP, Molden E, Asberg A, Mohebi BU, Ose L, et al. Exposure of atorvastatin is unchanged but lactone and acid metabolites are increased several-fold in patients with atorvastatin-induced myopathy. Clin Pharmacol Ther. 2006;79:532–9.
11. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–57.
12. Akerblom A, Wallentin L, Siegbahn A, Becker RC, Budaj A, Horrow J, et al. Outcome and causes of renal deterioration evaluated by serial cystatin C measurements in acute coronary syndrome patients—results from the PLATelet inhibition and patient Outcomes (PLATO) study. Am Heart J. 2012;164:728–34.
13. James S, Budaj A, Aylward P, Buck KK, Cannon CP, Cornel JH, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the platelet inhibition and patient outcomes (PLATO) trial. Circulation. 2010;122:1056–67.
14. Butler K, Teng R. Pharmacokinetics, pharmacodynamics, and safety of ticagrelor in volunteers with severe renal impairment. J Clin Pharmacol. 2012;52:1388–98.
15. Teng R, Mitchell PD, Butler KA. Pharmacokinetic interaction studies of co-administration of ticagrelor and atorvastatin or simvastatin in healthy volunteers. Eur J Clin Pharmacol. 2013;69:477–87.
16. Igel M, Sudhop T, von Bergmann K. Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors (statins). Eur J Clin Pharmacol. 2001;57:357–64.
17. Zhou D, Andersson TB, Grimm SW. In vitro evaluation of potential drug-drug interactions with ticagrelor: cytochrome P450 reaction phenotyping, inhibition, induction, and differential kinetics. Drug Metab Dispos Biol Fate Chem. 2011;39:703–10.
18. Teng R, Oliver S, Hayes MA, Butler K. Absorption, distribution, metabolism, and excretion of ticagrelor in healthy subjects. Drug Metab Dispos Biol Fate Chem. 2010;38:1514–21.
19. Sugidachi A, Ohno K, Ogawa T, Jakubowski J, Hashimoto M, Tomizawa A. A comparison of the pharmacological profiles of prasugrel and ticagrelor assessed by platelet aggregation, thrombus formation and haemostasis in rats. Br J Pharmacol. 2013;169:82–9.
20. Sirtori CR. The pharmacology of statins. Pharmacol Res. 2014;88:3–11.
21. Vree TB, Dammers E, Ulc I, Horkovics-Kovats S, Ryska M, Merkx I. Variable plasma/liver and tissue esterase hydrolysis of simvastatin in healthy volunteers after a single oral dose. Clin Drug Investig. 2001;21:643–52.
22. Prueksaritanont T, Gorham LM, Ma B, Liu L, Yu X, Zhao JJ, et al. In vitro metabolism of simvastatin in humans [SBT]identification of metabolizing enzymes and effect of the drug on hepatic P450s. Drug Metab Dispos Biol Fate Chem. 1997;25:1191–9.
23. Zhang T. Physiologically based pharmacokinetic modeling of disposition and drug-drug interactions for atorvastatin and its metabolites. Eur J Pharm Sci Off J Eur Fed Pharm Sci. 2015;77:216–29.
24. Jacobsen W, Kuhn B, Soldner A, Kirchner G, Sewing KF, Kollman PA, et al. Lactonization is the critical first step in the disposition of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor atorvastatin. Drug Metab Dispos Biol Fate Chem. 2000;28:1369–78.
25. Lennernäs H. Clinical pharmacokinetics of atorvastatin. Clin Pharmacokinet. 2003;42:1141–60.
26. Martin PD, Warwick MJ, Dane AL, Hill SJ, Giles PB, Phillips PJ, et al. Metabolism, excretion, and pharmacokinetics of rosuvastatin in healthy adult male volunteers. Clin Ther. 2003;25:2822–35.
27. Olsson AG, McTaggart F, Raza A. Rosuvastatin: a highly effective new HMG-CoA reductase inhibitor. Cardiovasc Drug Rev. 2002;20:303–28.
28. Varenhorst C, Eriksson N, Johansson Å, Barratt BJ, Hagström E, Åkerblom A, et al. Effect of genetic variations on ticagrelor plasma levels and clinical outcomes. Eur Heart J. 2015;36:1901–12.
29. Hagenbuch B, Meier PJ. Organic anion transporting polypeptides of the OATP/SLC21 family: phylogenetic classification as OATP/SLCO superfamily, new nomenclature and molecular/functional properties. Pflugers Arch. 2004;447:653–65.
30. Roth M, Obaidat A, Hagenbuch B. OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. Br J Pharmacol. 2012;165:1260–87.
31. König J, Cui Y, Nies AT, Keppler D. A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane. Am J Physiol Gastrointest Liver Physiol. 2000;278:G156–64.
32. Kellick K. Organic ion transporters and statin drug interactions. Curr Atheroscler Rep. 2017;19:65.
33. Kitamura S, Maeda K, Wang Y, Sugiyama Y. Involvement of multiple transporters in the hepatobiliary transport of rosuvastatin. Drug Metab Dispos Biol Fate Chem. 2008;36:2014–23.
34. SEARCH Collaborative Group, Link E, Parish S, Armitage J, Bowman L, Heath S, et al. SLCO1B1 variants and statin-induced myopathy—a genomewide study. N Engl J Med. 2008;359:789–99.
35. Brunham LR, Lansberg PJ, Zhang L, Miao F, Carter C, Hovingh GK, et al. Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. Pharmacogenom J. 2012;12:233–7.
36. Wang Y, Tian Y, Lv P, Chen L, Luo W, Jing X, et al. The effect of SLCO1B1polymorphism on the pharmacokinetics of atorvastatin and 2-hydroxyatorvastatin in healthy Chinese people. Pharm. 2017;72:365–8.
37. Danik JS, Chasman DI, MacFadyen JG, Nyberg F, Barratt BJ, Ridker PM. Lack of association between SLCO1B1 polymorphisms and clinical myalgia following rosuvastatin therapy. Am Heart J. 2013;165:1008–14.
38. Liu J-E, Liu X-Y, Chen S, Zhang Y, Cai L-Y, Yang M, et al. SLCO1B1 521T > C polymorphism associated with rosuvastatin-induced myotoxicity in Chinese coronary artery disease patients: a nested case-control study. Eur J Clin Pharmacol. 2017;73:1409–16.

39. Wessler JD, Grip LT, Mendell J, Giugliano RP. The P-glycoprotein transport system and cardiovascular drugs. J Am Coll Cardiol. 2013;61:2495–502.
40. Hochman JH, Pudvah N, Qiu J, Yamazaki M, Tang C, Lin JH, et al. Interactions of human P-glycoprotein with simvastatin, simvastatin acid, and atorvastatin. Pharm Res. 2004;21:1686–91.
41. Choi D-H, Choi J-S, Li C, Choi J-S. Effects of simvastatin on the pharmacokinetics of diltiazem and its main metabolite, desacetyldiltiazem, after oral and intravenous administration in rats: possible role of P-glycoprotein and CYP3A4 inhibition by simvastatin. Pharmacol Rep. 2011;63:1574–82.
42. Sieczkowski E, Lehner C, Ambros PF, Hohenegger M. Double impact on p-glycoprotein by statins enhances doxorubicin cytotoxicity in human neuroblastoma cells. Int J Cancer. 2010;126:2025–35.
43. Keskitalo JE, Kurkinen KJ, Neuvoneni PJ, Niemi M. ABCB1 haplotypes differentially affect the pharmacokinetics of the acid and lactone forms of simvastatin and atorvastatin. Clin Pharmacol Ther. 2008;84:457–61.
44. Chen C, Lin J, Smolarek T, Tremaine L. P-glycoprotein has differential effects on the disposition of statin acid and lactone forms in mdr1a/b knockout and wild-type mice. Drug Metab Dispos Biol Fate Chem. 2007;35:1725–9.
45. Chen C, Mireles RJ, Campbell SD, Lin J, Mills JB, Xu JJ, et al. Differential interaction of 3-hydroxy-3-methylglutaryl-coa reductase inhibitors with ABCB1, ABCC2, and OATP1B1. Drug Metab Dispos Biol Fate Chem. 2005;33:537–46.
46. Sakaeda T, Fujino H, Komoto C, Kakumoto M, Jin J-S, Iwaki K, et al. Effects of acid and lactone forms of eight HMG-CoA reductase inhibitors on CYP-mediated metabolism and MDR1-mediated transport. Pharm Res. 2006;23:506–12.
47. Sałacka A, Bińczak-Kuleta A, Kaczmarczyk M, Hornowska I, Safranow K. Clark JSC. Possible association of ABCB1:c.3435T > C polymorphism with high-density-lipoprotein-cholesterol response to statin treatment–a pilot study. Bosn J Basic Med Sci. 2014;14:144–9.
48. Becker ML, Visser LE, van Schaik RHN, Hofman A, Uitterlinden AG, Stricker BHC. Common genetic variation in the ABCB1 gene is associated with the cholesterol-lowering effect of simvastatin in males. Pharmacogenomics. 2009;10:1743–51.
49. Goard CA, Mather RG, Vinepal B, Clendening JW, Martirosyan A, Boutros PC, et al. Differential interactions between statins and P-glycoprotein: implications for exploiting statins as anticancer agents. Int J Cancer. 2010;127:2936–48.
50. Keskitalo JE, Kurkinen KJ, Neuvonen M, Backman JT, Neuvonen PJ, Niemi M. No significant effect of ABCB1 haplotypes on the pharmacokinetics of fluvastatin, pravastatin, lovastatin, and rosuvastatin. Br J Clin Pharmacol. 2009;68:207–13.
51. Zhou Q, Ruan Z-R, Yuan H, Xu D-H, Zeng S. ABCB1 gene polymorphisms, ABCB1 haplotypes and ABCG2 c.421c > A are determinants of inter-subject variability in rosuvastatin pharmacokinetics. Pharm. 2013;68:129–34.
52. Teng R, Butler K. A pharmacokinetic interaction study of ticagrelor and digoxin in healthy volunteers. Eur J Clin Pharmacol. 2013;69:1801–8.
53. Marsousi N, Doffey-Lazeyras F, Rudaz S, Desmeules JA, Daali Y. Intestinal permeability and P-glycoprotein-mediated efflux transport of ticagrelor in Caco-2 monolayer cells. Fundam Clin Pharmacol. 2016;30:577–84.
54. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. The Lancet. 2010;376:1320–8.
55. Goosen TC, Bauman JN, Davis JA, Yu C, Hurst SI, Williams JA, et al. Atorvastatin glucuronidation is minimally and nonselectively inhibited by the fibrates gemfibrozil, fenofibrate, and fenofibric acid. Drug Metab Dispos Biol Fate Chem. 2007;35:1315–24.
56. Prueksaritanont T, Zhao JJ, Ma B, Roadcap BA, Tang C, Qiu Y, et al. Mechanistic studies on metabolic interactions between gemfibrozil and statins. J Pharmacol Exp Ther. 2002;301:1042–51.
57. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. Drug Metab Dispos Biol Fate Chem. 2002;30:1280–7.
58. Williams JA, Hyland R, Jones BC, Smith DA, Hurst S, Goosen TC, et al. Drug-drug interactions for UDP-glucuronosyltransferase substrates: a pharmacokinetic explanation for typically observed low exposure (AUCi/AUC) ratios. Drug Metab Dispos Biol Fate Chem. 2004;32:1201–8.
59. Mrotzek SM, Rassaf T, Totzeck M. Ticagrelor leads to statin-induced rhabdomyolysis: a case report. Am J Case Rep. 2017;18:1238–41.
60. Kido K, Wheeler MB, Seratnahaei A, Bailey A, Bain JA. Rhabdomyolysis precipitated by possible interaction of ticagrelor with high-dose atorvastatin. J Am Pharm Assoc JAPhA. 2015;55:320–3.
61. Banakh I, Haji K, Kung R, Gupta S, Tiruvoipati R. Severe rhabdomyolysis due to presumed drug interactions between atorvastatin with amlodipine and ticagrelor. Case Rep Crit Care. 2017;2017:3801819.
62. Cenjor Martín R, Gutiérrez-Madrid E, Martín-Sánchez FJ, Cuervo Pinto R. Iatrogenic rhabdomyolysis in a patient with ischemic heart disease. Med Clin (Barc). 2016;146:e57–8.
63. Sarinic VM, Sandberg L, Hartman J, Caduff-Janosa P. Interaction between rosuvastatin and ticagrelor resulting in rhabdomyolysis. Upps. Monit. Cent. 2017. https://www.who-umc.org/media/164007/rhabdomyolysisweb.pdf. Accessed 4 Mar 2018.
64. van Vuren AJ, de Jong B, Bootsma HPR, Van der Veen MJ, Feith GW. Ticagrelor-induced renal failure leading to statin-induced rhabdomyolysis. Neth J Med. 2015;73:136–8.
65. Samuel G, Atanda AC, Onyemeh A, Awan A, Ajiboye O. A unique case of drug interaction between ticagrelor and statin leading to acute renal failure. Cureus. 2017;9:e1633.
66. Ronaldson KJ, O'Shea JM, Boyd IW. Risk factors for rhabdomyolysis with simvastatin and atorvastatin. Drug Saf. 2006;29:1061–7.
67. Khine H, Yuet WC, Adams-Huet B, Ahmad Z. Statin-associated muscle symptoms and SLCO1B1 rs4149056 genotype in patients with familial hypercholesterolemia. Am Heart J. 2016;179:1–9.
68. ZOCOR (simvastatin) Tablets—product information. merck.com. https://www.merck.com/product/usa/pi_circulars/z/zocor/zocor_pi.pdf. Accessed 4 Mar 2018.
69. Lipitor (atorvastatin calcium)—product information. pfizer.com. http://www.pfizer.com.au/sites/g/files/g10005016/f/201311/PI_Lipitor_355.pdf. Accessed 4 Mar 2018.
70. Crestor (rosuvastatin calcium)—product monograph. astrazeneca.ca. https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/crestor-product-monograph-en.pdf. Accessed 4 Mar 2018.
71. BRILINTA (ticagrelor)—Product Monograph. astrazeneca.ca. https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/BRILINTA%20-%20Product-Monograph.pdf. Accessed 4 Mar 2018.