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*Published in:*
British Journal of Clinical Pharmacology

*DOI:*
10.1111/bcp.15684

Published: 01/07/2023

*Document Version*
Final published version

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Link to publication

*Please cite the original version:*
Lehtisalo, M., Kiander, W., Filppula, A. M., Deng, F., Kidron, H., Korhonen, M., Sinkko, J., Koivula, K., & Niemi, M. (2023). Rhabdomyolysis during concomitant ticagrelor and rosuvastatin - a breast cancer resistance protein - mediated drug interaction? *British Journal of Clinical Pharmacology*, *89*(7), 2309-2315. https://doi.org/10.1111/bcp.15684

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Received: 18 November 2022 | Revised: 27 January 2023 | Accepted: 30 January 2023

DOI: 10.1111/bcp.15684

SHORT COMMUNICATION

# Rhabdomyolysis during concomitant ticagrelor and rosuvastatin: A breast cancer resistance protein-mediated drug interaction?

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**Funding information**
This study was supported by grants from the European Research Council (Grant agreement 725249), Sigrid Jusélius Foundation, State funding for university-level health research, and the Finnish Cultural Foundation (Helsinki, Finland).

[Correction added on 16 May 2023, after first online publication: The copyright has been changed.]

We present 3 patients diagnosed with rhabdomyolysis 1–6 months after the initiation of concomitant rosuvastatin and ticagrelor medication. A literature review and Food and Drug Administration adverse event reporting system revealed >40 reports of rhabdomyolysis during concomitant ticagrelor and rosuvastatin, including 3 with a fatal outcome. We show that ticagrelor inhibits breast cancer resistance protein-, organic anion transporting polypeptide (OATP) 1B1-, 1B3- and 2B1-mediated transport of rosuvastatin in vitro with half-maximal unbound inhibitory concentrations of 0.36, 4.13, 7.5 and 3.26 μM, respectively. A static drug interaction model predicted that ticagrelor may inhibit intestinal breast cancer resistance protein and thus increase rosuvastatin plasma exposure 2.1-fold, whereas the OATP-mediated hepatic uptake of rosuvastatin should not be inhibited due to relatively low portal ticagrelor concentrations. Taken together, concomitant use of ticagrelor with rosuvastatin may increase the systemic exposure to rosuvastatin and the risk of rosuvastatin-induced rhabdomyolysis. Further studies are warranted to investigate the potential pharmacokinetic interaction between ticagrelor and rosuvastatin in humans.

**KEYWORDS**
drug–drug-interaction, myotoxicity, rhabdomyolysis, rosuvastatin, ticagrelor

Minna Lehtisalo and Wilma Kiander contributed equally.

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## 1 | INTRODUCTION

Myotoxicity, varying from mild myalgia to potentially fatal rhabdomyolysis, is a well-known adverse effect of the cholesterol-lowering drug **rosuvastatin**.[1] The risk of rosuvastatin-induced muscle toxicity is dose dependent, and drug–drug interactions leading to increased plasma rosuvastatin concentrations increase the risk.

Rosuvastatin is commonly used concomitantly with the platelet aggregation inhibitor ticagrelor to prevent recurrent cardiovascular events, e.g., after a percutaneous coronary intervention. The treatment is usually well tolerated. However, clinicians have reported multiple cases of rhabdomyolysis during concomitant use of rosuvastatin and ticagrelor,[2–12] leading to a growing suspicion of an underlying drug–drug interaction. Three cases were recently identified and are described in this article for the first time.

Rosuvastatin undergoes only limited metabolism, and metabolizing enzymes have only minor effect on rosuvastatin exposure.[13] In contrast, several transporters, e.g., **organic anion transporting polypeptides** (OATPs) 1B1, 1B3 and 2B1, and **breast cancer resistance protein** (BCRP, official name ABCG2), markedly affect rosuvastatin pharmacokinetics.[1,14] Inhibitors of these transporters have been shown to increase rosuvastatin exposure. For example, in a randomized placebo-controlled cross-over study in healthy volunteers, febuxostat increased rosuvastatin exposure 1.9-fold, probably by inhibiting intestinal BCRP.[15] A recent case report highlighted a possibly OATP1B-mediated interaction between canagliflozin and rosuvastatin resulting in rhabdomyolysis.[16] Reduced-function variants in the BCRP-encoding *ABCG2* and the OATP1B1-encoding *SLCO1B1* genes are also associated with increased rosuvastatin concentrations and increased risk of adverse reactions.[17–20]

Since rosuvastatin-induced myotoxicity is a potentially life-threatening condition and concomitant use of rosuvastatin and ticagrelor is common, we found it important to investigate the possible drug–drug interaction of rosuvastatin and ticagrelor. The aim of this study was to report 3 new cases of rosuvastatin-induced rhabdomyolysis in patients receiving ticagrelor and rosuvastatin concomitantly, and to identify potential pharmacokinetic interactions underlying the adverse reaction.

### What is already known about this subject

- Myotoxicity is a concentration-dependent adverse effect of statins.
- Rosuvastatin is commonly used concomitantly with ticagrelor to prevent recurrent cardiovascular events.
- Clinicians have reported multiple cases of rhabdomyolysis during concomitant use of rosuvastatin and ticagrelor, leading to a growing suspicion of an underlying drug–drug interaction.

### What this study adds

- We present 3 new cases of rhabdomyolysis possibly following a ticagrelor–rosuvastatin interaction.
- Based on our in vitro and static prediction studies, inhibition of intestinal breast cancer resistance protein by ticagrelor may double rosuvastatin plasma concentrations.
- Concomitant use of ticagrelor with rosuvastatin may increase the systemic exposure to rosuvastatin and risk of rosuvastatin-induced rhabdomyolysis.

## 2 | METHODS

### 2.1 | Patient cases

We present 3 patients, who received treatment for rhabdomyolysis after receiving ticagrelor and rosuvastatin concomitantly. Their information was obtained from electronic medical records after written informed consent. The collected data include demographic information, medical history, medication, details of the current condition including physical examination, laboratory, electrocardiogram and imaging findings, and details of the management and outcome of the condition.

For the purposes of this study, the patients were genotyped for the *SLCO1B1* c.388A > G (rs2306283, p.N130D), c.463C>A (rs11045819, p.P155T), c.521T>C (rs4149056, p.Val174Ala), c.1929A>C (rs34671512, p.L643F) and *ABCG2* c.421C>A (rs2231142, p.Q141K) single nucleotide variants (Supporting information). The nomenclature of genes and gene products in this article conforms to the CONCISE GUIDE TO PHARMACOLOGY. Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.[21]

A literature search of previous reports of rhabdomyolysis during concomitant use of rosuvastatin and ticagrelor was conducted in PubMed and the Food and Drug Administration adverse events reporting system (FAERS; Supporting information).[22]

### 2.2 | In vitro studies

To investigate the potential mechanism of the ticagrelor-rosuvastatin interaction, we performed in vitro experiments to determine the effects of ticagrelor on the most relevant rosuvastatin-transporting proteins, i.e., OATP1B1, OATP1B3, OATP2B1 and BCRP, in OATP-overexpressing human embryonic kidney cells and BCRP-overexpressing membrane vesicles, essentially as described previously.[15,23] To take into account the unspecific binding of ticagrelor during the experiments, the fraction of unbound ticagrelor in the inhibition studies was examined with rapid equilibrium dialysis device. The in vitro methods are described in more detail in Supporting information.

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### 2.3 | Static drug–drug interaction predictions

Based on the obtained in vitro inhibition data, we carried out static interaction predictions between ticagrelor and rosuvastatin using the equations and rosuvastatin parameters reported previously (Tables S1 and S2).[24,25] In addition, we carried out control predictions where we investigated the interactions between febuxostat (BCRP inhibitor) and rosuvastatin, rifampicin (BCRP, OATP1B1, OATP1B3 and OATP2B1 inhibitor) and rosuvastatin, and ticagrelor and simvastatin acid (OATP1B1 and CYP3A4 substrate) using our previous data and literature data (Tables S1–S3).[15,26–28]

## 3 | RESULTS

### 3.1 | Patient cases

#### 3.1.1 | Patient A

A 70–80-year-old man presented in hospital due to ventricular tachycardia (Figure 1). He had severe walking difficulties and was diagnosed with rhabdomyolysis. The patient had history of anterior ST elevation myocardial infarction followed by mural thrombus and stroke, and he had been resuscitated from ventricular fibrillation 2 months earlier. Rosuvastatin had been initiated 7 weeks before diagnosis of rhabdomyolysis and ticagrelor 4 weeks later, following a percutaneous coronary intervention (PCI). Recovery from PCI had been complicated by elevated creatinine levels and walking difficulties. Following diagnosis of rhabdomyolysis, dialysis was initiated and renal function started to recover after a month.

#### 3.1.2 | Patient B

A woman in her early 80s was diagnosed with rhabdomyolysis after suffering from increasing muscle pain since a falling incident. A month earlier she had been treated in hospital due to unstable angina pectoris, and rosuvastatin and ticagrelor had been initiated. Simvastatin therapy had been discontinued earlier for unknown reason. The patient recovered after rosuvastatin discontinuation with 11 days treatment in hospital. Kidney function remained good during the episode of rhabdomyolysis.

#### 3.1.3 | Patient C

A 60–70-year-old woman was referred to hospital due to anuria, nausea and vomiting. Her plasma creatinine concentration was 1014 μmol/L. Six months earlier she had undergone PCI due to non-ST elevation myocardial infarction, and ticagrelor and rosuvastatin had been initiated. After diagnosis of rhabdomyolysis, rosuvastatin and ticagrelor were discontinued. The patient was treated in intensive care unit, and kidney function recovered without dialysis.

### 3.2 | Literature review

In the literature, we found a total of 11 reported cases of rhabdomyolysis during concomitant treatment with ticagrelor and rosuvastatin (Table S4).[2–12] The patients (7 female, 4 male) were aged 49–87 years. The daily dose of rosuvastatin was 20–40 mg, and daily dose of ticagrelor 90–180 mg. Time to rhabdomyolysis onset from the start of concomitant medication was 2 weeks to 8 months (median 1.75 months).

The search of the FAERS revealed 44 cases of rhabdomyolysis during concomitant treatment with rosuvastatin and ticagrelor (Table S5). Thirty-two percent occurred in patients older than 75 years, 11.4% were considered life-threatening and 6.8% had been fatal.

### 3.3 | Mechanistic studies

Ticagrelor inhibited OATP1B1, 1B3 and 2B1, and BCRP-mediated rosuvastatin uptake into human embryonic kidney cells or membrane vesicles with half-maximal unbound inhibitory concentrations of 0.36, 4.13, 7.5 and 3.26 μM (Figure 2). According to static drug–drug interaction predictions, ticagrelor-mediated BCRP inhibition in the intestine may increase plasma exposure to rosuvastatin 2.1-fold (Figure 2). Inhibition of OATP1B1, OATP1B3 and OATP2B1 by ticagrelor was predicted to have no effect on rosuvastatin concentrations due to relatively low portal concentrations of ticagrelor. Inhibition of OATPs and BCRP by rifampicin (positive control) was predicted to increase rosuvastatin AUC 2.5-fold (intravenous rifampicin) and 4.9-fold (oral rifampicin), consistent with previously published clinical data.[26,27] Inhibition of intestinal but not hepatic CYP3A4 by 180 mg ticagrelor was predicted to increase simvastatin acid AUC 1.9-fold, slightly overpredicting the clinically observed 1.5-fold interaction.[28]

## 4 | DISCUSSION

In this article, we present 3 patient cases, where rhabdomyolysis occurred during concomitant use of ticagrelor with rosuvastatin, and mechanistic studies investigating the possible interaction between the 2 drugs. In the cases, symptoms and diagnosis of rhabdomyolysis occurred within 1–6 months after the initiation of rosuvastatin and ticagrelor, and in all cases the condition resolved after discontinuation of rosuvastatin. Our in vitro data and static prediction studies suggest that ticagrelor inhibits BCRP-mediated efflux of rosuvastatin in the small intestine and may double rosuvastatin plasma concentrations. This indicates that ticagrelor could increase the myotoxicity of rosuvastatin via a pharmacokinetic interaction.

BCRP limits the oral bioavailability of rosuvastatin by mediating the efflux of rosuvastatin in the small intestine. Our data show that ticagrelor inhibits BCRP with a half-maximal inhibitory concentration of 0.36 μM. According to our prediction, a dose of 90 mg ticagrelor may thus lead to a 2.1-fold increase of rosuvastatin plasma exposure. A similar effect on rosuvastatin exposure has been seen in healthy

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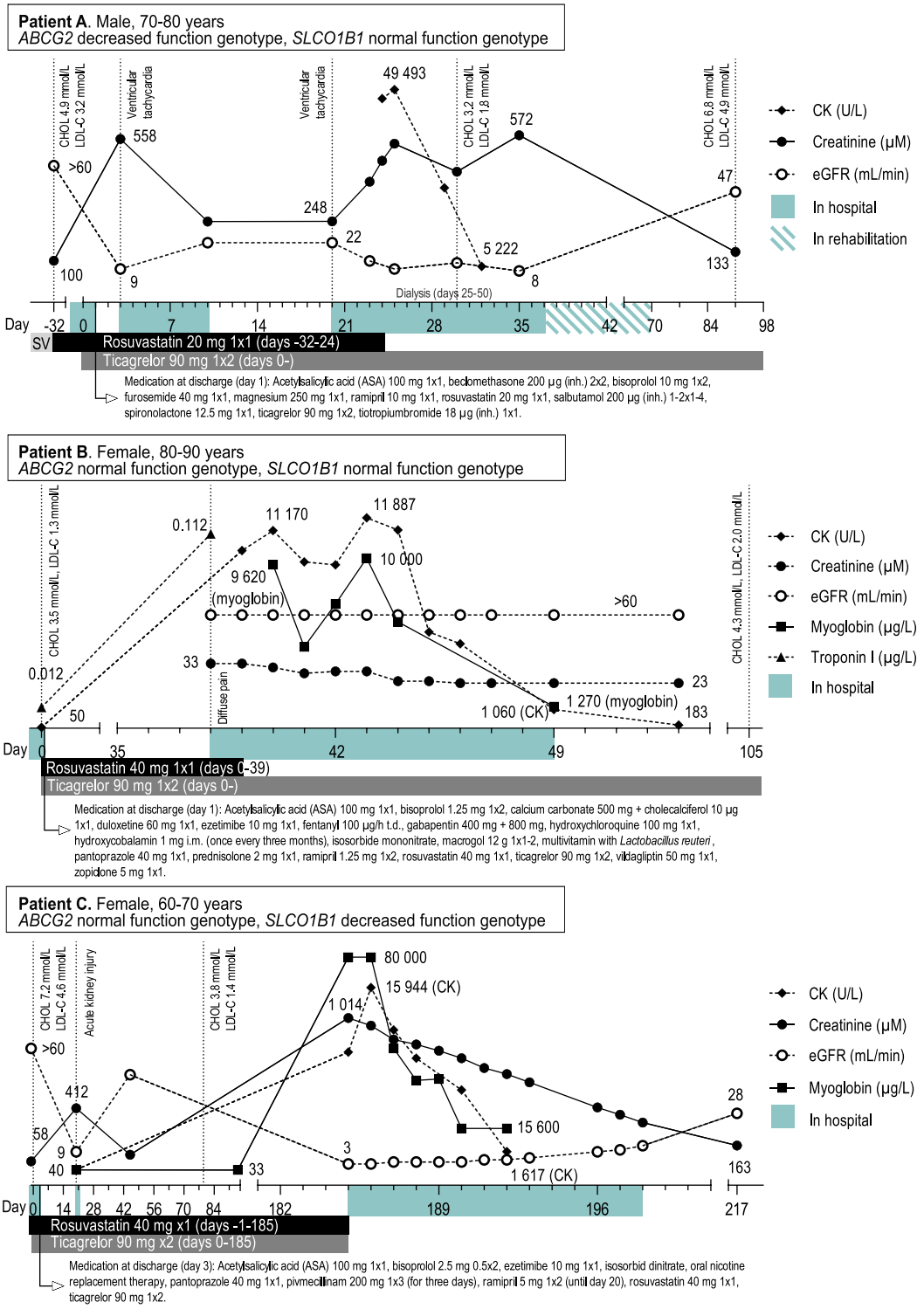


**FIGURE 1** Details of the 3 patients diagnosed with rhabdomyolysis after concomitant treatment with rosuvastatin and ticagrelor. CHOL, cholesterol; CK, creatinine kinase; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; SV, simvastatin.

volunteers for another BCRP-inhibiting drug, febuxostat.[15] The effects of the inhibitors on BCRP in the liver were not evaluated in the predictions, as clinical data suggest limited effects of hepatic BCRP activity alteration on the overall pharmacokinetics of rosuvastatin.[18,20]

OATPs are another important group of rosuvastatin transporting proteins. They mediate the uptake of rosuvastatin into hepatocytes for further elimination. Previous case reports have discussed that an OATP-mediated interaction of ticagrelor and rosuvastatin could be the mechanism underlying the increased risk rhabdomyolysis.[6,12] However, our data and static predictions indicate that while ticagrelor inhibits OATP-mediated rosuvastatin transport in vitro, this interaction should not increase rosuvastatin exposure in humans due to relatively low

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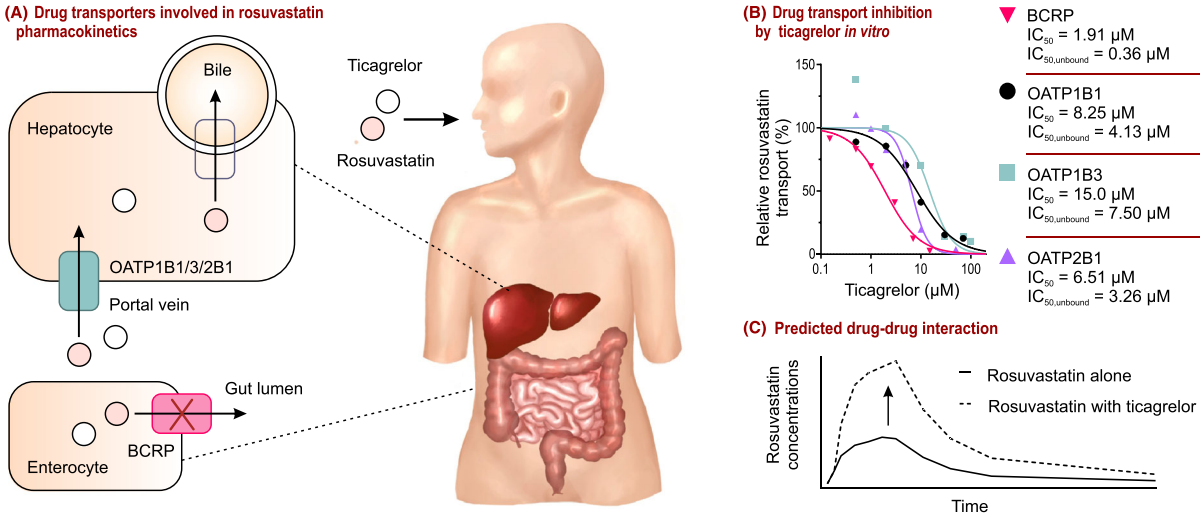


**(D) Predicted increase in rosuvastatin or simvastatin acid area under the plasma concentration-time curve (AUC) due to transporter or CYP enzyme inhibition**

| Perpetrator drug, dose | Victim drug | Predicted fold increase in AUC due to inhibition of individual pathways | | | | | | Overall predicted fold increase in AUC | Clinically observed fold increase in AUC |
|---|---|---|---|---|---|---|---|---|---|
| | | BCRP (gut) | CYP3A4 (gut) | OATP1B1 | OATP1B3 | OATP2B1 | CYP3A4 (liver) | | |
| Ticagrelor | | | | | | | | | |
| 90 mg | Rosuvastatin | 1.98 | n/a | 1.03 | 1.00 | 1.01 | n/a | 2.1 | n/a |
| 180 mg | Simvastatin acid | n/a | 1.58 | 1.12 | n/a | n/a | 1.06 | 1.9 | 1.5 |
| Febuxostat | | | | | | | | | |
| 20 mg | Rosuvastatin | 1.99 | n/a | n/a | n/a | n/a | n/a | 2.0 | 1.9 |
| Rifampicin | | | | | | | | | |
| 600 mg infusion | Rosuvastatin | n/a | n/a | 1.57 | 1.12 | 1.15 | n/a | 2.5 | 3.0-3.3 |
| 600 mg po | Rosuvastatin | 1.77 | n/a | 1.62 | 1.13 | 1.17 | n/a | 4.9 | 4.4 |

**FIGURE 2** Results of in vitro and prediction studies investigating the mechanism of the possible drug–drug-interaction between ticagrelor and rosuvastatin. The pink cylinder depicts BCRP, and the green cylinder, OATPs 1B1, 1B3 and 2B1. AUC, area under the plasma concentration-time curve; BCRP, breast cancer resistance protein; $IC_{50}$, half-maximal inhibitory concentration; $IC_{50,unbound}$, $IC_{50}$ value corrected for nonspecific binding; OATP, organic anion transporting polypeptide.

ticagrelor concentrations in the portal vein. Our predictions of the interaction between ticagrelor and simvastatin acid support the lack of clinically relevant inhibition of hepatic OATPs by ticagrelor.

Genetic variance in the BCRP-encoding *ABCG2* gene and the OATP1B1-encoding *SLCO1B1* gene may affect rosuvastatin concentrations, and reduced-function variants in these genes are known to increase rosuvastatin exposure. For example, homozygosity for the *ABCG2* c.421C>A or the *SLCO1B1* c.521T>C single nucleotide variants more than doubles rosuvastatin exposure,[18,20] which is similar to the effect of BCRP inhibition by ticagrelor in our predictions. The Clinical Pharmacogenetics Implementation Consortium guideline recommends using lower doses of rosuvastatin for patients who have genetically decreased or poor BCRP or OATP1B1 function.[19] One of our patients was genotyped after the rhabdomyolysis as having decreased BCRP function and another as decreased OATP1B1 function, which may have further increased rosuvastatin exposure. The decreased BCRP and OATP1B1 function phenotypes are relatively common (approximately 13 and 28% of the Finnish population).[20]

The risk of statin-induced myotoxicity is dose-dependent.[29] An 80-mg dose of rosuvastatin, investigated during drug development, seemed to multiply the risk of developing significantly increased creatine kinase concentrations compared with a 40-mg dose.[30] Like in our patients, the reported dose of rosuvastatin has been high (20–40 mg) in previous cases of rhabdomyolysis during concomitant ticagrelor and rosuvastatin (Table S4). The interaction potential of ticagrelor and rosuvastatin should be considered especially when starting high intensity rosuvastatin treatment.

Other risk factors for rosuvastatin-induced myotoxicity include increased age, multimorbidity and renal impairment. Concomitant use of ticagrelor and rosuvastatin is quite common, and usually the combination is used without severe adverse effects.[31] Patients who experience severe statin-induced myotoxicity often have many risk factors concomitantly, which was also the case with our patients. Multiple risk factors may also contribute to the variation in the onset time of rosuvastatin-induced rhabdomyolysis. Statin-induced musculoskeletal symptoms usually develop within 2–4 weeks of starting the statin, but they can also occur after years of stable medication.[32] The range of onset times in our patients was 1–6 months, and, in the literature, 2 weeks to 8 months after starting concomitant treatment with ticagrelor and rosuvastatin.

In previous case reports, the mechanism underlying the interaction has been suggested to be e.g., ticagrelor-induced acute renal impairment leading to decreased excretion of rosuvastatin, or cytochrome P450 (CYP) enzyme-mediated interactions.[2–4,7,9,10,12] In 1 of our cases, no kidney injury was observed during the episode of rhabdomyolysis, and in another case, renal function recovered after rosuvastatin cessation and dialysis while ticagrelor was continued. These findings suggest that the possible renal impairment may be a consequence rather than cause of rhabdomyolysis. CYP enzymes, by contrast, play only a minor

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role in rosuvastatin pharmacokinetics, as it is mainly excreted unchanged. Therefore, it is unlikely that a CYP-mediated interaction should be causing the reported incidents of rhabdomyolysis.

This study has some limitations. Since rosuvastatin plasma concentrations from our patients are not available, the conclusions of this study are solely based on in vitro and static prediction studies. Therefore, they should be interpreted with caution. In the predictions, we could not take into consideration the effect of OATP2B1 inhibition in the gut. OATP2B1 may play a role in the absorption processes of drugs in the intestine, but the evidence is contradictory and its role in rosuvastatin absorption is unclear. Therefore, we evaluated only the effects of inhibition of hepatic OATP2B1 on rosuvastatin concentrations.

In the FAERS database, >40 rhabdomyolysis cases can be identified as possibly following a ticagrelor–rosuvastatin interaction. The database consists of self-reported data, and although we only included cases reported by health care professionals in our analyses, the risk of reporting bias is obvious. Furthermore, identifying duplicate reports is difficult due to lacking information. Therefore, the true incidence of rhabdomyolysis or a causation between ticagrelor–rosuvastatin combination and increased risk of rhabdomyolysis cannot be concluded from these data. However, the reports could be seen as a signal of a potential drug–drug interaction.

To conclude, ticagrelor inhibits intestinal BCRP-mediated efflux of rosuvastatin. This may lead to doubling of systemic rosuvastatin concentrations and increased risk of rhabdomyolysis. Further studies are warranted to investigate the potential pharmacokinetic interaction in humans.

## CONTRIBUTORS

M.L., W.K., A.M.F., K.K. and M.N. wrote the manuscript; M.L., W.K., A.M.F., F.D., H.K., K.K. and M.N. designed the research; M.L., W.K., A.M.F., F.D., H.K., M.K., J.S., K.K. and M.N. performed the research; M.L., W.K., K.K. and M.Ni. analysed the data.

## ACKNOWLEDGEMENTS

This study was supported by grants from the European Research Council (Grant agreement 725249), Sigrid Jusélius Foundation, and State funding for university-level health research (Helsinki, Finland). W.K. was supported by a grant from the Finnish Cultural Foundation (Helsinki, Finland).

## COMPETING INTERESTS

All authors declared no competing interests for this work.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available to the extent allowed by the EU General Data Protection Regulation, other applicable regulation and participant consent from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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**How to cite this article:** Lehtisalo M, Kiander W, Filppula AM, et al. Rhabdomyolysis during concomitant ticagrelor and rosuvastatin: A breast cancer resistance protein-mediated drug interaction? *Br J Clin Pharmacol*. 2023;89(7):2309-2315. doi:10.1111/bcp.15684

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