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Ticagrelor Increases Exposure to the Breast Cancer Resistance Protein Substrate Rosuvastatin

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Ticagrelor and rosuvastatin are often used concomitantly after atherothrombotic events. Several cases of rhabdomyolysis during concomitant ticagrelor and rosuvastatin have been reported, suggesting a drug–drug interaction. We showed recently that ticagrelor inhibits breast cancer resistance protein (BCRP) and organic anion transporting polypeptide (OATP) 1B1, 1B3, and 2B1-mediated rosuvastatin transport *in vitro*. The aim of this study was to investigate the effects of ticagrelor on rosuvastatin pharmacokinetics in humans. In a randomized, crossover study, 9 healthy volunteers ingested a single dose of 90 mg ticagrelor or placebo, followed by a single 10 mg dose of rosuvastatin 1 hour later. Ticagrelor 90 mg or placebo were additionally administered 12, 24, and 36 hours after their first dose. Ticagrelor increased rosuvastatin area under the plasma concentration-time curve (AUC) and peak plasma concentration 2.6-fold (90% confidence intervals: 1.8–3.8 and 1.7–4.0, $P = 0.001$ and $P = 0.003$), and prolonged its half-life from 3.1 to 6.6 hours ($P = 0.009$). Ticagrelor also decreased the renal clearance of rosuvastatin by 11% (3%–19%, $P = 0.032$). The N-desmethylrosuvastatin:rosuvastatin AUC_{0-10h} ratio remained unaffected by ticagrelor. Ticagrelor had no effect on the plasma concentrations of the endogenous OATP1B substrates glycodeoxycholate 3-O-glucuronide, glycochenodeoxycholate 3-O-glucuronide, glycodeoxycholate 3-O-sulfate, and glycochenodeoxycholate 3-O-sulfate, or the sodium-taurocholate cotransporting polypeptide substrate taurocholic acid. These data indicate that ticagrelor increases rosuvastatin concentrations more than twofold in humans, probably mainly by inhibiting intestinal BCRP. Because the risk for rosuvastatin-induced myotoxicity increases along with rosuvastatin plasma concentrations, using ticagrelor concomitantly with high doses of rosuvastatin should be avoided.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Several cases of rhabdomyolysis during concomitant rosuvastatin and ticagrelor have been reported. In a previous study, ticagrelor inhibited breast cancer resistance protein and organic anion transporting polypeptide 1B1, 2B1, and 1B3-mediated rosuvastatin transport *in vitro*.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We investigated the effects of ticagrelor on the pharmacokinetics of rosuvastatin in healthy volunteers. In addition, we investigated the effects of ticagrelor on endogenous organic anion transporting polypeptide 1B and sodium-taurocholate cotransporting polypeptide biomarkers.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Ticagrelor increases the exposure to rosuvastatin on average 2.6-fold in healthy volunteers. The mechanism of the interaction is likely to be inhibition of intestinal BCRP.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Ticagrelor may increase the risk of rosuvastatin-induced muscle symptoms, especially at high rosuvastatin doses. Clinicians should take this interaction into consideration when it is necessary to use a high-intensity statin and platelet inhibitor concomitantly.

Rosuvastatin is one of the most common 3-hydroxy-3-methylglutaryl coenzyme A inhibitors used in the treatment of hypercholesterolemia. Although usually well-tolerated, rosuvastatin can cause muscle symptoms of varying severity, especially at higher doses.[1] Previously published case reports have suggested that concomitant use of rosuvastatin and the platelet-inhibitor ticagrelor may have

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led to severe, even fatal, cases of rosuvastatin-induced rhabdomyolysis.[2–13] Because the risk of rosuvastatin-induced myotoxicity is concentration-dependent, the rhabdomyolysis cases suggest a potential pharmacokinetic drug–drug interaction between ticagrelor and rosuvastatin.

Rosuvastatin is excreted mainly unchanged into urine and bile. Inhibition of drug metabolizing enzymes is therefore unlikely to significantly affect rosuvastatin exposure.[1,14,15] In contrast, membrane transporter proteins, most importantly breast cancer resistance protein (BCRP), organic anion transporting polypeptides (OATP), and sodium-taurocholate cotransporting polypeptide (NTCP), play an important role in rosuvastatin pharmacokinetics.[1,16] The BCRP-inhibiting drug febuxostat increased plasma rosuvastatin concentrations more than twofold in healthy volunteers.[17] Darolutamide, an inhibitor of BCRP, OATP1B1, and OATP1B3, has increased rosuvastatin exposure 5.2-fold.[18] Furthermore, a single oral dose of the OATP- and BCRP-inhibitor rifampicin has increased rosuvastatin concentrations more than fourfold.[19] Similarly, genetically poor BCRP or OATP1B1 function associate with markedly increased rosuvastatin concentrations.[20–23]

We recently showed that ticagrelor inhibits BCRP, OATP1B1, 1B3, and 2B1 *in vitro* (half-maximal inhibitory concentrations 0.36, 4.13, 7.50, and 3.26 μM).[13] Due to low portal vein concentrations of ticagrelor, the inhibition of hepatic OATPs is, however, unlikely to be clinically relevant. By contrast, inhibition of intestinal BCRP was predicted to cause a 2.1-fold increase in rosuvastatin exposure.

Rosuvastatin and ticagrelor are commonly used concomitantly in the secondary prevention of atherothrombotic events, but previous data suggest that they may have an interaction leading to an increased risk of rosuvastatin-induced myotoxicity. Therefore, we found it important to study whether the suggested drug–drug interaction between ticagrelor and rosuvastatin has a pharmacokinetic basis. We conducted a randomized, placebo-controlled crossover study to investigate the effects of ticagrelor on rosuvastatin pharmacokinetics in healthy volunteers. To further investigate the mechanism of this interaction, we also investigated the effects of ticagrelor on endogenous biomarkers of OATP1B and NTCP transporters.

METHODS

Subjects and study design

Nine healthy White Finnish volunteers (6 women and 3 men, with a mean ± standard deviation age 24 ± 5 years, height 174 ± 11 cm, weight 64 ± 11 kg, and body mass index 21 ± 2 kg/m^2) entered the study after giving written informed consent. All participants were healthy, as confirmed by medical history, physical examination, and routine laboratory tests. The participants did not use any continuous medication, including hormonal contraception, and they were all nonsmokers. The study protocol was approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District (record number HUS/2836/2021) and the Finnish Medicines Agency Fimea (EudraCT number 2019-002440-24). The study has been registered at the ClinicalTrials.gov database with the identifier NCT05373277.

In a randomized, placebo-controlled, crossover study with two phases, the participants ingested as a pretreatment placebo (placebo tablets; University Pharmacy, Helsinki, Finland), or 90 mg ticagrelor (Brilique; AstraZeneca UK Ltd., Cheshire, UK) twice daily (8 AM and 8 PM, with 150 mL water) after an overnight fast on days 1 and 2. A single oral 10 mg dose of rosuvastatin (Crestor; AstraZeneca UK Ltd.) was administered at 9 AM on day 1, exactly 1 hour after the first dose of the pretreatment. There was a washout period of at least 2 weeks between the 2 phases. A standardized warm meal was served 4 hours, and light meals 7 and 10 hours after rosuvastatin ingestion. Use of any other drugs was prohibited from 1 week before to 1 week after the day of rosuvastatin administration, the use of alcohol from 1 day before to 2 days after the day of rosuvastatin administration, and the use of grapefruit products throughout the whole study.

Timed venous blood samples (4 or 9 mL each) were collected prior to and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 23, and 47 hours after the ingestion of rosuvastatin to EDTA-containing tubes. The tubes were placed on ice immediately after sampling, and plasma was separated from the samples within 30 minutes. Urine was collected up to 10 hours after rosuvastatin administration. The plasma and urine aliquots were stored at −70°C until analysis.

Analysis of drug and endogenous biomarker concentrations

Rosuvastatin, N-desmethyl rosuvastatin, ticagrelor, and the isotope labeled internal standards rosuvastatin-D6, N-desmethyl rosuvastatin-D6, and ticagrelor-D7 were purchased from Toronto Research Chemicals (North York, ON, Canada). Prior to plasma sample analysis, plasma (150 μL) proteins were precipitated with acetonitrile (450 μL) containing the internal standards, and the sample mixture was drawn through the Phree Phospholipid Removal 96-well extraction plate (Phenomenex, Torrance, CA) according to the manufacturer's protocol. For the analysis of urine samples, a 150 μL aliquot of urine was diluted with 300 μL of 10 mM ammonium formate (pH 3.9, adjusted with glacial formic acid) containing the internal standards, and extracted using Waters 10 mg HLB plate (Waters Corp., Milford, MA). In brief, the urine sample mixture was loaded into the preconditioned extraction plate, washed with 100 μL of 5% methanol and extracted 2 times with 100 μL acetonitrile. Regarding both plasma and urine sample preparation, the supernatant was evaporated, and the residue was reconstituted in 100 μL of 0.1% formic acid:acetonitrile (80:20, v:v). Drug concentrations were measured using a Sciex 5500 QTRAP liquid chromatography–tandem mass spectrometry (LC-MS/MS) system (AB Sciex, Toronto, ON, Canada). The chromatographic separation was achieved on a Luna C18 Polar (100 × 2.1 mm internal diameter) analytical column (Phenomenex) using 5 mM ammonium formate (pH 3.9) and acetonitrile as mobile phase for the channels A and B, respectively. The flow rate and the column temperature were set at 300 μL/min and 40°C. The mobile phase gradient profile was set as follows: 1 minute at 20% B, then a linear ramp to 40% B over 2 minutes, a second linear ramp to 90% B over 2 minutes, and 1 minute at 90% B on hold before the equilibration step back to the starting composition (20% B). The mass spectrometer was operated in positive multiple reaction monitoring mode for rosuvastatin (mass-to-charge ratio (m/z) 482–258), and in negative mode for N-desmethyl rosuvastatin (m/z 466–404), ticagrelor (m/z 521–361), and C124910XX (m/z 477–361). Ticagrelor-D7 served as an internal standard for C124910XX and the concentration was expressed in arbitrary units (C124910XX peak area/ticagrelor-D7 peak area) using a signal-to-noise ratio > 50 as quantification limit. For rosuvastatin, N-desmethyl rosuvastatin, and ticagrelor, the lower limits of quantification were 0.2, 0.5, and 10 ng/mL. The between-day precisions (expressed as coefficient of variation) and accuracies of the quality control samples were < 15% and within ±15% for all analytes at relevant concentrations.

The concentrations of the endogenous OATP1B and NTCP biomarkers glycochenodeoxycholate 3-O-glucuronide (GCDCA-3G), glycodeoxycholate 3-O-glucuronide (GDCA-3G), glycochenodeoxycholate 3-O-sulfate (GCDCA-3S), glycodeoxycholate 3-O-sulfate (GDCA-3S), and taurocholic acid (TCA) were determined in plasma samples collected before and 55 minutes and 4 hours after the first administration of ticagrelor or placebo on day 1. The reference TCA and the internal standard, TCA-D7, were purchased from Cayman Chemical (Ann Arbor, MI).

GDCA-3G, GCDCA-3G, GDCA-3S, and GCDCA-3S, and the corresponding stable isotope-labeled internal standards were kindly provided by the Pfizer Corporation. Plasma samples were prepared using a protein precipitation,[24] and the simultaneous quantification of biomarkers was performed on a Sciex 6,500 QTRAP+ LC-MS/MS system (AB Sciex) as previously described,[25] with the following modifications. The flow rate was 0.65 mL/min and the column temperature was held at 55°C. The mobile phase (channel A 0.1% formic acid and channel B 0.1% formic acid in acetonitrile) gradient consisted of an initial hold of 20% B for 0.5 minutes, followed by a linear ramp to 30% B over 3 minutes, followed by a second linear ramp to 70% B over 1.3 minutes, and 1.6 minutes at 98% B on hold, before a return to initial conditions (20% B). TCA was quantified using the ion transition m/z 514 to 124. The lower limits of quantification for TCA, GDCA-3G, GCDCA-3G, GDCA-3S, and GCDCA-3S were 0.4, 1.0, 0.5, 0.5, and 0.5 ng/mL, respectively. The quality control samples prepared in charcoal purified plasma (high, medium, and low levels) showed between-day ($n = 6$) precisions below 15% and accuracies within ±15% for each analyte.

Pharmacokinetics

We calculated the peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$), AUC from zero to 10 or 11 hours (AUC_{0-10h} or AUC_{0-11h}), elimination half-life ($t_{½}$), amount excreted into urine (*Ae*), and renal clearance (Cl_{renal}) of rosuvastatin, N-desmethylrosuvastatin, ticagrelor, and C124910XX by standard noncompartmental methods using Phoenix WinNonlin, version 8.2 (Certara, Princeton, NJ).

Genotyping

Genomic DNA was extracted from buffy coats using the Maxwell 16 LEV Blood DNA Kit on a Maxwell 16 Research automated nucleic acid extraction system (Promega, Madison, WI). The participants were genotyped for the *ABCG2* c.421C>A (rs2231142, p.Q141K) and *SLCO1B1* c.388A>G (rs2306283, p.N130D), c.521T>C (rs4149056, p.V174A), and c.1929A>C (rs34671512, p.L463F) single nucleotide variants with a clinical pharmacogenetic panel test available at the Genetics laboratory of the HUS Diagnostic Center (Helsinki University Hospital, Helsinki, Finland), as described previously.[13] *SLCO1B1* *-alleles were named according to the Pharmacogene Variation Consortium core allele definitions.[26]

Statistical analysis

The number of participants was estimated to be sufficient to detect a potentially clinically meaningful difference of 30% in the $AUC_{0-\infty}$ of rosuvastatin between the 2 phases with a power of 80% (α-level 5%). The statistical analyses were carried out using IBM SPSS Statistics for Windows, version 29 (Armonk, NY). The analyzed pharmacokinetic parameters and the concentrations and concentration ratios of endogenous biomarkers were logarithmically transformed before the analyses. Statistical comparisons between the phases were made using repeated-measures analysis of variance with treatment phase as a within-subjects factor. Correlations between the AUC_{0-11h} and C_{max} of ticagrelor and the fold-change in the rosuvastatin $AUC_{0-\infty}$ and C_{max} were tested with Pearson's correlation. The P values < 0.05 were considered statistically significant. The results are presented as geometric means with geometric coefficient of variation or 90% confidence intervals (CIs), except for T_{max}, which is presented as median with range.

Static interaction model

Static interaction predictions between ticagrelor and rosuvastatin were carried out using the equations and rosuvastatin parameters reported previously (**Tables S1, S2**).[13,27–36] For prediction of the effect of ticagrelor on renal BCRP, unbound C_{max} of ticagrelor was used.

Table 1 Effects of ticagrelor on the pharmacokinetics of rosuvastatin

Variable	Placebo phase	Ticagrelor phase	Ticagrelor phase to placebo phase ratio (90% CI); *P* value
Rosuvastatin			
C_{max} (ng/mL)	5.3 (91%)	13.7 (56%)	2.57 (1.67–3.95); $P=0.003$
T_{max} (h)	5.0 (1.5–6.0)	2.0 (1.0–4.0)	$P=0.065$
$t_{1/2}$ (h)	3.1 (52%)	6.6 (38%)	2.14 (1.42–3.23); $P=0.009$
$AUC_{0-\infty}$ (ng·h/mL)	34.3 (70%)	90.0 (51%)	2.62 (1.81–3.81); $P=0.001$
$AUC_{0-10\,h}$ (ng·h/mL)	28.9 (73%)	71.6 (52%)	2.47 (1.76–3.48); $P=0.001$
Ae (mg)	0.33 (91%)	0.72 (72%)	2.19 (1.52–3.15); $P=0.004$
Cl_{renal} (mL/min)	191 (55%)	169 (46%)	0.89 (0.81–0.97); $P=0.032$
N-desmethyl rosuvastatin			
C_{max} (ng/mL)	1.29 (30%)	2.25 (61%)	1.74 (1.07–2.83), $P=0.07$
T_{max} (h)	3.5 (1.5–5)	3.0 (1.5–5)	$P=0.59$
$AUC_{0-10\,h}$ (ng·h/mL)	5.31 (38%)	10.20 (70%)	1.92 (1.21–3.04), $P=0.035$
N-desmethyl rosuvastatin:rosuvastatin $AUC_{0-10\,h}$ ratio	0.13 (35%)	0.13 (18%)	1.02 (0.84–1.24); $P=0.84$
Ae (mg)	0.09 (101%)	0.17 (60%)	2.02 (1.37–2.97); $P=0.010$
Cl_{renal} (mL/min)	444 (37%)	344 (36%)	0.78 (0.58–1.04); P=0.14

The pretreatments in the 2 phases were a single dose of placebo or 90 mg ticagrelor at 8 AM and 8 PM on days 1 and 2. Rosuvastatin 10 mg was administered at 9 AM on day 1. Data are given as geometric mean with geometric coefficient of variation, except for T_{max}, which is given as median with range. The geometric mean ratios between the phases are given with 90% CI. For N-desmethyl rosuvastatin, three individuals had plasma concentrations below the quantification limit in the placebo phase and were excluded from the analyses, except for the Ae.

Ae, amount excreted into urine; $AUC_{0-\infty}$, area under the plasma concentration-time curve from 0 to infinity; $AUC_{0-10\,h}$, AUC from 0 to 10 hours; CI, confidence interval; Cl_{renal}, renal clearance; C_{max}, peak plasma concentration; $t_{1/2}$, terminal half-life; T_{max}, time to C_{max}.

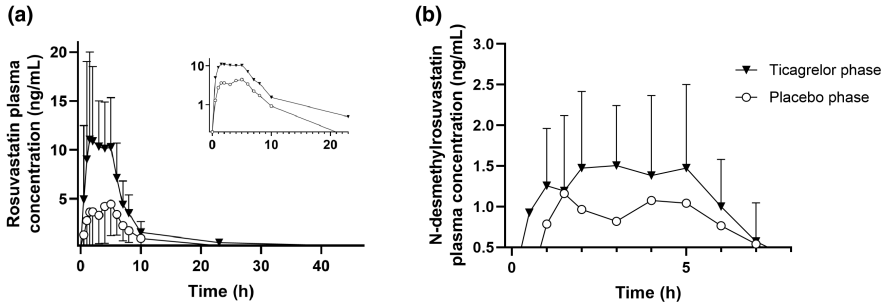

Figure 1 The effect of ticagrelor on the plasma concentrations of (**a**) rosuvastatin and (**b**) N-desmethyl rosuvastatin. In a randomized, crossover study, nine healthy volunteers ingested as pre-treatment a 90 mg dose of ticagrelor or placebo, followed by a single 10 mg dose of rosuvastatin 1 hour later. Ticagrelor 90 mg or placebo were additionally administered 12, 24, and 36 hours after their first dose. Data are geometric means with geometric coefficient of variation. For clarity, some error bars have been omitted. The inset depicts the plasma concentrations of rosuvastatin on a semilogarithmic scale.

RESULTS

Effect of ticagrelor on rosuvastatin pharmacokinetics and endogenous biomarkers

Ticagrelor increased both the C_{max} and $AUC_{0-\infty}$ of rosuvastatin 2.6-fold (90% CI: 1.8–3.8 and 1.7–4.0, $P = 0.003$, and $P = 0.003$), and the *Ae* of rosuvastatin 2.2-fold (90% CI: 1.5–3.2, $P = 0.001$), compared with placebo (**Table 1**, **Figure 1**). The $t_{½}$ of rosuvastatin was prolonged from 3.1 to 6.6 hours ($P = 0.009$) in the ticagrelor phase. Ticagrelor also decreased the Cl_{renal} of rosuvastatin by 11% (3%–19%, $P = 0.032$).

Three individuals had N-desmethylrosuvastatin plasma concentrations below the quantification limit in the placebo phase and were excluded from the pharmacokinetic analyses of N-desmethyl rosuvastatin, except for the *Ae*. Ticagrelor increased the AUC_{0-10h} and *Ae* of N-desmethyl rosuvastatin 1.9-fold (1.2–3.0, $P = 0.035$) and 2.0-fold (1.4–3.0, $P = 0.01$), but had no effect on the N-desmethyl rosuvastatin:rosuvastatin AUC_{0-10h} ratio (**Table 1**).

Two individuals were genotyped as having *SLCO1B1* genotypes (**1/*15* and **15/*37*) that predict decreased OATP1B1 function. None carried the *ABCG2* c.421C>A single nucleotide variation (SNV). The individuals with genetically decreased OATP1B1 function appeared to have a larger $AUC_{0-\infty}$ of rosuvastatin than those individuals with normal OATP1B1 function, but there were no clear differences in the extent of interaction between the genotypes (**Figure 2**). Ticagrelor had no effect on the plasma concentrations of GCDCA-3G, GDCA-3G, GCDCA-3S, GDCA-3S, or TCA (**Table 2**).

Static interaction modeling

Ticagrelor-mediated inhibition of the intestinal and renal BCRP was predicted to cause a 2.0-fold increase in rosuvastatin AUC (**Table 3**). According to our model, inhibition of OATP1B1, OATP1B3, and OATP2B1 by ticagrelor should have no effect on rosuvastatin concentrations. In our previously published static interaction model,[13] we did not include renal BCRP, as it has been unclear whether renal BCRP has any role in the pharmacokinetics of rosuvastatin. In this clinical study, however, we saw a decrease in the Cl_{renal} of rosuvastatin in the ticagrelor phase. Therefore, we also included renal BCRP in the model. In the static interaction model, the inhibition of renal BCRP by ticagrelor was predicted to have no effect on the AUC of rosuvastatin.

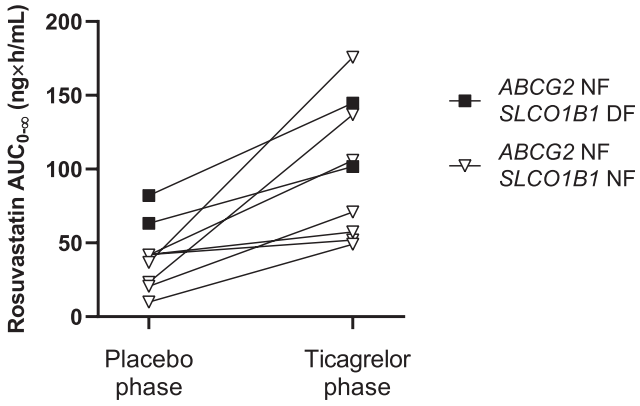

Figure 2 The individual rosuvastatin area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) values in a cross-over study with two phases, where nine healthy volunteers ingested either a 90 mg dose of ticagrelor or placebo, followed by a single 10 mg dose of rosuvastatin 1 hour later. Ticagrelor 90 mg or placebo were additionally administered 12, 24, and 36 hours after their first dose. AUC, area under the plasma concentration-time curve; DF, decreased function; NF, normal function.

Ticagrelor pharmacokinetics

The C_{max} and AUC_{0-11h} of ticagrelor varied 3.0- and 3.3-fold, and those of the ticagrelor metabolite C124910XX 2.5-fold and 4.7-fold between individuals (**Figure 3**, **Table 4**). The fold-change of C_{max} or $AUC_{0-\infty}$ of rosuvastatin between the two phases did not correlate with ticagrelor AUC_{0-11h} ($r^2 = 0.013$ and $r^2 = 0.003$, $P = 0.77$ and $P = 0.88$) or C_{max} ($r^2 = 0.049$ and $r^2 = 0.021$, $P = 0.57$ and $P = 0.71$).

DISCUSSION

Earlier *in vitro* and prediction data as well as published case reports of rosuvastatin-induced rhabdomyolysis during concomitant ticagrelor treatment have suggested a pharmacokinetic drug–drug interaction between rosuvastatin and ticagrelor. The present study shows that ticagrelor increases rosuvastatin plasma exposure on average 2.6-fold. Ticagrelor also had a minor effect on the Cl_{renal} of rosuvastatin, but did not affect N-desmethyl rosuvastatin:rosuvastatin AUC ratio or the concentrations of endogenous OATP1B or NTCP substrates.

Table 2 Effects of ticagrelor on the plasma concentrations of OATP1B and NTCP biomarkers

Variable	Placebo phase	Ticagrelor phase	Ticagrelor phase to placebo phase ratio (90% CI); *P* value
GDCA-3G			
C_0 (ng/mL)	38.5 (145%)	33.1 (118%)	0.86 (0.48–1.55); *P*=0.64
C_{55min} (ng/mL)	40.8 (98%)	36.4 (79%)	0.89 (0.64–1.24); *P*=0.53
C_{4h} (ng/mL)	23.6 (140%)	21.6 (115%)	0.91 (0.58–1.45); *P*=0.73
C_{55min}:C_0 ratio	1.06 (73%)	1.10 (44%)	1.04 (0.61–1.76); *P*=0.90
C_{4h}:C_0 ratio	0.61 (56%)	0.65 (42%)	1.06 (0.69–1.64); *P*=0.79
GCDCA-3G			
C_0 (ng/mL)	18.3 (129%)	15.7 (97%)	0.86 (0.51–1.43); *P*=0.59
C_{55min} (ng/mL)	20.5 (78%)	17.7 (65%)	0.86 (0.62–1.19); *P*=0.42
C_{4h} (ng/mL)	13.1 (103%)	10.7 (98%)	0.81 (0.56–1.18); *P*=0.33
C_{55min}:C_0 ratio	1.12 (73%)	1.13 (39%)	1.00 (0.61–1.66); *P*=0.98
C_{4h}:C_0 ratio	0.72 (71%)	0.68 (39%)	0.95 (0.58–1.55); *P*=0.85
GDCA-3S			
C_0 (ng/mL)	59.7 (77%)	53.5 (58%)	0.90 (0.52–1.55); *P*=0.72
C_{55min} (ng/mL)	58.4 (43%)	60.7 (49%)	1.04 (0.73–1.48); *P*=0.84
C_{4h} (ng/mL)	44.0 (95%)	46.9 (67%)	1.07 (0.59–1.92); *P*=0.85
C_{55min}:C_0 ratio	0.98 (52%)	1.13 (50%)	1.16 (0.81–1.67); *P*=0.47
C_{4h}:C_0 ratio	0.74 (71%)	0.88 (48%)	1.19 (0.77–1.83); *P*=0.48
GCDCA-3S			
C_0 (ng/mL)	36.3 (63%)	32.8 (109%)	0.90 (0.53–1.54); *P*=0.73
C_{55min} (ng/mL)	36.0 (50%)	40.5 (90%)	1.12 (0.86–1.47); *P*=0.45
C_{4h} (ng/mL)	27.8 (64%)	28.2 (115%)	1.01 (0.59–1.75); *P*=0.96
C_{55min}:C_0 ratio	0.99 (59%)	1.23 (56%)	1.25 (0.85–1.83); *P*=0.32
C_{4h}:C_0 ratio	0.77 (67%)	0.86 (46%)	1.12 (0.78–1.62); *P*=0.57
TCA			
C_0 (ng/mL)	7.82 (66%)	10.77 (173%)	1.38 (0.56–3.40); *P*=0.53
C_{55min} (ng/mL)	8.69 (100%)	11.42 (155%)	1.31 (0.73–2.37); *P*=0.41
C_{4h} (ng/mL)	2.52 (140%)	4.21 (118%)	1.67 (0.82–3.42); *P*=0.22
C_{55min}:C_0 ratio	1.11 (120%)	1.06 (69%)	0.95 (0.50–1.82); *P*=0.90
C_{4h}:C_0 ratio	0.32 (140%)	0.39 (74%)	1.21 (0.62–2.37); *P*=0.60

The pretreatments in the 2 phases were a single dose of placebo or 90 mg ticagrelor at 8 AM and 8 PM on days 1 and 2. Rosuvastatin 10 mg was administered at 9 AM on day 1.

Data are given as geometric mean with geometric coefficient of variation. The geometric mean ratios between the phases are given with 90% CI.

C_0, concentration before ticagrelor or placebo administration; C_{55min}, concentration 55 minutes after ticagrelor or placebo administration, C_{4h}, concentration 4 hours after ticagrelor or placebo administration; CI, confidence interval; GDCA-3G, glycodeoxycholic acid 3-O-glucuronide; GDCA-3S, glycodeoxycholate acid 3-sulfate; GCDCA-3G, glycochenodeoxycholic acid 3-O-glucuronide; GCDCA-3S, glycochenodeoxycholic acid 3-sulfate; NTCP, sodium taurocholate cotransporting polypeptide; OATP1B, organic anion transporting polypeptide 1B; TCA, taurocholic acid.

Taken together, these data indicate a pharmacokinetic, likely BCRP-mediated interaction that may have contributed to the reported cases of rhabdomyolysis during concomitant ticagrelor and rosuvastatin.

The findings that ticagrelor increased the concentrations of rosuvastatin without a major effect on the elimination of rosuvastatin and with no effect on the N-desmethyl rosuvastatin:rosuvastatin AUC ratio suggest that ticagrelor increased the oral bioavailability of rosuvastatin. A plausible mechanism of this interaction is inhibition of BCRP-mediated rosuvastatin efflux in the small intestine. In a previous clinical study, the BCRP-inhibiting drug febuxostat increased the C_{max} and AUC of rosuvastatin 2.1-fold and 1.9-fold.[17] Similarly, the *ABCG2* c.421A/A

Table 3 Predicted increase in rosuvastatin AUC due to transporter inhibition by 90 mg ticagrelor

Predicted fold increase in rosuvastatin AUC due to inhibition of individual pathways	
BCRP (gut)	1.98
BCRP (kidneys)	1.00
OATP1B1 (liver)	1.01
OATP1B3 (liver)	1.00
OATP2B1 (liver)	1.00
Overall predicted fold increase in AUC	2.02
Clinically observed fold increase in AUC	2.62

AUC, area under the plasma concentration-time curve.

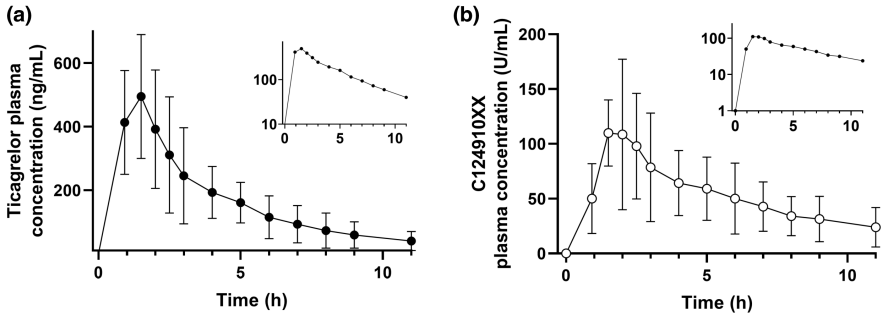

Figure 3 The concentrations of (**a**) ticagrelor and (**b**) C124910XX after administration of 90 mg ticagrelor. Data are geometric means with geometric coefficients of variation. Insets depict the same data on a semilogarithmic scale.

Table 4 Pharmacokinetic variables of ticagrelor and its metabolite, C124910XX, in healthy volunteers, after a single oral dose of 90 mg ticagrelor

	C_{max} (ng/mL)[a]	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)[a]	AUC_{0-11h} (ng·h/mL)[a]
Ticagrelor	526 (36%)	1.5 (0.9–2.0)	2.8 (21%)	2,091 (43%)	1,921 (41%)
C124910XX	126 (30%)	2.0 (0.9–2.0)	4.5 (33%)	778 (50%)	605 (41%)

Data are given as geometric mean with geometric coefficient of variation, except for T_{max}, which is given as median with range.
$AUC_{0-\infty}$, area under the plasma concentration-time curve from 0 to infinity; $AUC_{0-10\,h}$, AUC from 0 to 10 hours; C_{max}, peak plasma concentration; T_{max}, time to C_{max}.
[a]Except for C124910XX, for which C_{max} and $AUC_{0-\infty}$ are in arbitrary units, U/mL or U·h/mL.

genotype that predicts poor BCRP function has been associated with a 2.0–2.2-increased AUC of rosuvastatin.[22,37] The effect size of ticagrelor on rosuvastatin pharmacokinetics in this study was in the vicinity of these previous findings. According to our static interaction model, inhibition of intestinal BCRP by ticagrelor would increase the plasma exposure to rosuvastatin on average twofold.[13] This is well within 2-fold of the observed value 2.6, which is a commonly applied criterion for accuracy of drug–drug interaction predictions. The results of this clinical study therefore confirm that the static interaction model works well when the properties of drugs are well-established.

In addition to BCRP, ticagrelor also inhibits the OATP1B1-, OATP1B3-, and OATP2B1-mediated rosuvastatin transport *in vitro*. Due to relatively low ticagrelor concentrations in the portal vein, our static model predicted that hepatic OATP inhibition is not clinically relevant. In the clinical study, ticagrelor had no effect on the plasma concentrations of the endogenous OATP1B substrates GDCA-3G, GCDCA-3G, GDCA-3S, and GCDCA-3S confirming the prediction as these compounds have been shown to be highly sensitive OATP1B biomarkers.[24,38] The plasma concentrations of GCDCA-3G and GDCA-3G have been shown to increase even in the presence of weak OATP1B1 inhibition.[39] Ticagrelor also had no effect on taurocholic acid, which is a known, highly sensitive NTCP substrate. For example, myrcludex B, a drug used to treat hepatitis B and D, completely blocks NTCP and has increased the plasma concentrations of taurocholic acid up to 124-fold.[40] Taken together, these findings indicate that hepatic OATP1B1, 1B3, and 2B1 play no major role in the ticagrelor-rosuvastatin interaction. In addition, ticagrelor inhibits P-glycoprotein and CYP3A4,[33] but these proteins play no significant role in the pharmacokinetics of rosuvastatin.[1,14,41] Therefore, BCRP-inhibition is the most likely mechanism of the ticagrelor-rosuvastatin interaction.

The Cl_{renal} of rosuvastatin was slightly decreased by ticagrelor. Because rosuvastatin is excreted primarily into the feces,[31] the observed 11% decrease in Cl_{renal} would alone explain only a 3% increase in the AUC of rosuvastatin. The clinical relevance of this decrease is therefore minimal. When we used the pharmacokinetic data of ticagrelor from the present study in the static interaction model and included renal BCRP in the model,[42] we found that inhibition of renal BCRP by ticagrelor should have a negligible effect on the AUC of rosuvastatin.

In our study, two individuals were genotyped as having *SLCO1B1* genotypes that predict decreased OATP1B1 function. The sample size is too small to make analyses of the effects of genetic variants on the interaction. In addition, there were no participants with genotypes that predict poor OATP1B1 function phenotype. The individuals with the genotype-predicted decreased OATP1B1 function seemed, however, to have slightly higher than average rosuvastatin concentrations in both phases. Patients with genotypes that predict poor OATP1B1 function are likely to have higher baseline rosuvastatin exposures and are, therefore, also more susceptible to the clinical consequences of BCRP inhibition by ticagrelor.[16,18,22,23]

The platelet inhibitors ticagrelor, clopidogrel, and prasugrel are all used after atherothrombotic events, such as myocardial infarction or unstable angina pectoris. Because the efficacy of the prodrug clopidogrel is largely affected by the patient's *CYP2C19* metabolizer status,[43] ticagrelor has been widely preferred to ensure effective anti-platelet therapy. On the other hand, rosuvastatin is an alternative to atorvastatin, when the patient needs a high-intensity statin, as is the case after an atherothrombotic event. Our findings indicate a potential risk of adverse effects when the patient receives ticagrelor and rosuvastatin concomitantly.

Because rosuvastatin has linear pharmacokinetics, it could be estimated that the ticagrelor-induced 2.6-fold increase of rosuvastatin

exposure at the recommended maximum dose of 40 mg daily would equal the average exposure following a 104 mg daily rosuvastatin dose. According to the US Food and Drug Administration (FDA) approval package of Crestor, during the drug development, the 80 mg dose of rosuvastatin was already associated with a markedly greater incidence of myotoxicity than the 40 mg or lower doses.[44] Accordingly, when used concomitantly with ticagrelor, a maximum dose of 10 mg rosuvastatin could be recommended to mitigate the increased risk of myotoxicity. This is consistent with the current dosing recommendations for patients who use drugs that are known to increase rosuvastatin concentrations more than twofold, but not more than fourfold, such as velpatasvir or atazanavir/ritonavir.[45,46] It is worth noticing that interindividual variation in the rosuvastatin pharmacokinetics decreased markedly in the ticagrelor phase. In fact, all the individual AUC values in the ticagrelor phase were less than double the single highest AUC value in the placebo phase. However, because there is likely more interindividual variation between patients in real life than among our healthy volunteers, caution is warranted, and the 10 mg daily dose should be a safe option.

Inhibition of intestinal BCRP should affect the hepatic concentrations of rosuvastatin to the same extent as the plasma concentrations. Because liver is rosuvastatin's site of action, the efficacy of rosuvastatin should therefore also increase when BCRP is inhibited during ticagrelor treatment. This notion is supported by pharmacogenomic studies, where impaired BCRP function has been associated with an increased cholesterol-lowering effect of rosuvastatin. For example, in the JUPITER trial, an intronic *ABCG2* SNV in a strong linkage disequilibrium with the decreased-function c.421C>A SNV was associated with a larger reduction in low-density lipoprotein cholesterol levels in patients receiving 20 mg of rosuvastatin.[47] Therefore, rosuvastatin could be used at a reduced dose with ticagrelor without loss of cholesterol-lowering efficacy, and a 10 mg daily dose could be considered high-intensity statin treatment when ticagrelor is used concomitantly.

The patients who receive high doses of rosuvastatin and ticagrelor concomitantly have usually had an atherothrombotic event and often undergone a percutaneous coronary intervention or a cardiac bypass. These patients are already predisposed to more statin-related adverse effects through, for example, impaired renal function, increased age, multimorbidity, high statin dose, and polypharmacotherapy. There is also likely more interindividual variation in the interaction than in our group of young healthy volunteers. Even with our homogenous group of healthy participants, the extent of interaction varied markedly between individuals. The largest observed increases in rosuvastatin C_{max} and AUC were approximately sixfold. The effect of ticagrelor on rosuvastatin concentrations in some patients may therefore be much larger than the average 2.6-fold increase observed in this study.

In addition to rosuvastatin, two other statins, atorvastatin and fluvastatin, are known BCRP substrates. Therefore, ticagrelor may also increase their concentrations. In previous clinical studies, individuals homozygous for the *ABCG2* c.421C>A single nucleotide variant had 1.7-fold increased AUCs of fluvastatin and atorvastatin when compared with non-carriers of the variant.[21,37] In a previous drug interaction study, ticagrelor increased the C_{max} of atorvastatin by 23% and $AUC_{0-\infty}$ by 36%.[33] A few case reports of rhabdomyolysis during concomitant ticagrelor and atorvastatin treatment have also been published.[48]

In addition to ticagrelor, both clopidogrel and prasugrel have been shown to moderately inhibit BCRP *in vitro*.[49] Clopidogrel has been shown to increase the AUC of rosuvastatin 2-fold after administration of a 300 mg loading dose and 1.4-fold after repeated administration of a 75 mg dose.[50] However, there seem to be no studies investigating possible effects of prasugrel on the pharmacokinetics of rosuvastatin.

To conclude, ticagrelor increased rosuvastatin exposure on average 2.6-fold, probably by inhibiting intestinal BCRP. It may therefore increase the risk for rosuvastatin-induced myotoxicity. This drug–drug interaction may have contributed to the cases where patients have developed rhabdomyolysis during concomitant ticagrelor and rosuvastatin. When it is necessary to use a high-intensity statin and platelet inhibitor concomitantly, clinicians should be aware of this possible interaction and consider using rosuvastatin in lower doses, combined with ezetimibe if needed, or choosing another statin or platelet aggregation inhibitor.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

M.L. and M.Ni. wrote the manuscript. M.L., M.H., and M.Ni. designed the research. M.L., E.K.T., M.Ne., J.I.K., O.L.-R., A.M.F., M.K., J.T.B., and M.Ni. performed the research. M.L. and M.Ni. analyzed the data.

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