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Using Pharmacovigilance Data for Signal Detection of Drug Interactions for Rosuvastatin

Ronja Levomäki[1] | Päivi Hirvensalo[2] | Aleksi Tornio[2,3] | Anne M. Filppula[1]

[1]Pharmaceutical Sciences Laboratory, Department of Natural and Health Sciences, the Faculty of Science and Engineering, Åbo Akademi University, Turku, Finland | [2]Integrative Physiology and Pharmacology, Institute of Biomedicine, University of Turku, Turku, Finland | [3]Unit of Clinical Pharmacology, Turku University Hospital, Turku, Finland

Correspondence: Anne M. Filppula (anne.filppula@abo.fi)

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ABSTRACT

The 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor rosuvastatin is a substrate of breast cancer resistance protein (BCRP). BCRP inhibition increases rosuvastatin plasma concentrations and may result in concentration-dependent muscle toxicity, at worst rhabdomyolysis. We investigated if concomitant use of rosuvastatin and drugs identified as in vitro BCRP inhibitors shows an increased number of rhabdomyolysis events based on pharmacovigilance data. From reports in the US Food and Drug Administration Adverse Event Reporting System for patients using rosuvastatin, we formed interaction (rosuvastatin with inhibitor) and non-interaction (rosuvastatin without inhibitor) groups for 71 BCRP inhibitors. These groups were further divided into subgroups with or without rhabdomyolysis. For each inhibitor, we calculated reporting odds ratio (ROR) and 95% confidence intervals (CIs). We identified 9777 individual rosuvastatin-related reports during 2013–2023, including 815 rhabdomyolysis reports. Of the 71 inhibitors, 19 had enough reports for analysis. Significantly increased RORs were obtained for the clinical BCRP inhibitors febuxostat (ROR 2.47, 95% CI 1.38–4.43) and ticagrelor (ROR 4.15, 95% CI 3.32–5.20). Amiodarone, erlotinib and rifampicin showed significantly increased RORs. Our findings support known interactions involving febuxostat and ticagrelor and suggest that also other BCRP inhibitors may increase the risk of rosuvastatin-induced rhabdomyolysis.

1 | Introduction and Background

Rosuvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, is widely prescribed for the treatment of hypercholesterolaemia and prevention of cardiovascular events. Unlike many other statins, rosuvastatin undergoes minimal hepatic metabolism and is primarily excreted unchanged into the bile and urine [1]. The pharmacokinetics of rosuvastatin is markedly affected by membrane transport proteins, particularly breast cancer resistance protein (BCRP), organic anion transporting polypeptides (OATPs) and sodium-taurocholate cotransporting polypeptide (NTCP) [1, 2]. OATP1B1, OATP1B3, OATP2B1 and, to a lesser extent, NTCP facilitate hepatic uptake, whereas BCRP primarily mediates the intestinal efflux of rosuvastatin, limiting its bioavailability [1, 3, 4].

Many drugs that inhibit BCRP increase rosuvastatin exposure significantly. For example, in healthy volunteers, ticagrelor has increased the area under the plasma concentration–time curve (AUC) of rosuvastatin by 2.6-fold [5], whereas febuxostat has increased rosuvastatin AUC by 1.9-fold [6], supporting a BCRP-mediated drug–drug interaction (DDI). Similarly, compounds such as capmatinib [7], fenebrutinib [8], and fostamatinib [9] have also been shown to increase rosuvastatin exposure in clinical DDI studies, likely due to BCRP inhibition. Interestingly, recent in vitro data have identified several previously unrecognized

Plain Language Summary

The cholesterol-lowering drug rosuvastatin is a substrate of breast cancer resistance protein (BCRP). BCRP inhibition increases rosuvastatin plasma concentrations, which may result in rhabdomyolysis, severe muscle toxicity. Using pharmacovigilance data, we investigated if concomitant use of rosuvastatin and BCRP inhibitors results in an increased number of rhabdomyolysis events. We identified 9777 rosuvastatin-related reports, including 815 rhabdomyolysis reports. Of the 19 inhibitors with enough data, significantly increased reporting odds ratios were obtained for amiodarone, erlotinib, febuxostat, rifampicin and ticagrelor. Our findings support known interactions involving febuxostat and ticagrelor and suggest that other BCRP inhibitors may also increase the rosuvastatin-induced rhabdomyolysis risk.

moderate to strong BCRP inhibitors among approved drugs [10]. Although in vitro inhibition does not necessarily translate into clinically relevant in vivo interactions, these findings raise concerns about potential unknown interactions in clinical practice.

Although rosuvastatin is generally well tolerated, it is associated with dose- and concentration-dependent muscle toxicity. Adverse effects vary from mild myalgia to severe rhabdomyolysis, which can be life threatening [1, 11]. Several case reports have linked rhabdomyolysis to the concomitant use of ticagrelor and rosuvastatin [12–15], suggesting that an increase in rosuvastatin plasma concentrations by ticagrelor may translate into an elevated risk of rosuvastatin-induced muscle toxicity.

Because of these previous findings, we wanted to investigate if similar associations exist in real-world data also for other BCRP inhibitor drugs used concomitantly with rosuvastatin. In this study, data from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), a large spontaneous reporting database, were utilized to investigate potential DDI signals for rosuvastatin. Specifically, we studied whether the concomitant use of rosuvastatin and drugs identified as strong BCRP inhibitors in vitro [10] is associated with an increased reporting frequency of rhabdomyolysis, suggesting clinically relevant transporter-mediated interactions.

2 | Materials and Methods

We used the publicly available FAERS database to retrieve adverse event reports where rosuvastatin was included as a suspected drug. We investigated DDI pairs involving rosuvastatin as the victim drug and 70 compounds that have previously been listed as strong inhibitors of BCRP in vitro (Table S1) [10]. Known clinical BCRP inhibitors ticagrelor (one of the listed inhibitors) and febuxostat were used as positive controls, resulting in a total of 71 compounds studied as inhibitors. Rhabdomyolysis was selected as the adverse event of interest and disproportionality analysis was used to assess the associations between concomitant drug use and the occurrence of rhabdomyolysis. The study was conducted in accordance with the *Basic & Clinical Pharmacology & Toxicology* policy for experimental and clinical studies [16].

2.1 | Data Search and Handling

A search in FAERS dashboard was conducted to retrieve adverse event reports for rosuvastatin. The search included both generic and brand names. To ensure all studied BCRP inhibitors were on the market when the adverse events were reported, we restricted the dataset to reports received between Q1 2013 and Q4 2023.

The raw data were prepared manually for data analysis as follows: Reports from other sources than healthcare professionals were excluded, as the studied adverse event, rhabdomyolysis, requires clinical confirmation. To minimize bias due to duplicate reports, a strict predefined protocol was implemented for duplicate exclusion. The most recent report was selected for analysis if it contained the most comprehensive information regarding medication and patient identifiers. In some cases, duplicate reports were merged to maximize completeness of medication details, patient identifiers and event date.

Next, reports containing the inhibitors of interest were identified. For each individual inhibitor, reports mentioning use of the inhibitor were included in the interaction group. All other reports (including those with rosuvastatin listed as the only drug in use) were included in the non-interaction group. Both the interaction and non-interaction groups were further divided into subgroups with reports including rhabdomyolysis and those involving all other adverse events (Table 1).

2.2 | Data Analysis

The distribution of reports into subgroups and data analysis were done separately for each studied inhibitor. For each inhibitor, the four distinct subgroups (a–d; Table 1) formed the basis for the reporting odds ratio (ROR) analysis. RORs were calculated to quantify interaction signals and a 95% confidence interval (CI) was applied to ensure statistical robustness. The RORs and 95% CIs were calculated using the following two equations:

TABLE 1 | The adverse event reports for rosuvastatin were distributed into four subgroups for the ROR analysis based on the two-by-two contingency table.

	Adverse event present (rhabdomyolysis)	Adverse event absent (all other adverse reactions)
Interaction group (with inhibitor)	a	b
Non-interaction group (all other drugs)	c	d

$$ROR = (a / c) / (b / d)$$

$$95\,\%\,CI = e^{\ln(ROR)\pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

The increased risk for rhabdomyolysis was considered statistically significant if the lower limit of the 95% CI exceeded 1 and the number of cases in the interaction subgroup where rhabdomyolysis was present (subgroup a) was ≥ 3. After an initial analysis, an adjusted analysis was carried out to assess whether the positive controls febuxostat and ticagrelor were disproportionately influencing the results. In the adjusted analysis, all reports containing febuxostat or ticagrelor were excluded from both interaction and non-interaction subgroups. However, in the case of febuxostat, all reports containing ticagrelor were excluded and vice versa. Following the exclusion, adjusted RORs and 95% CIs were calculated.

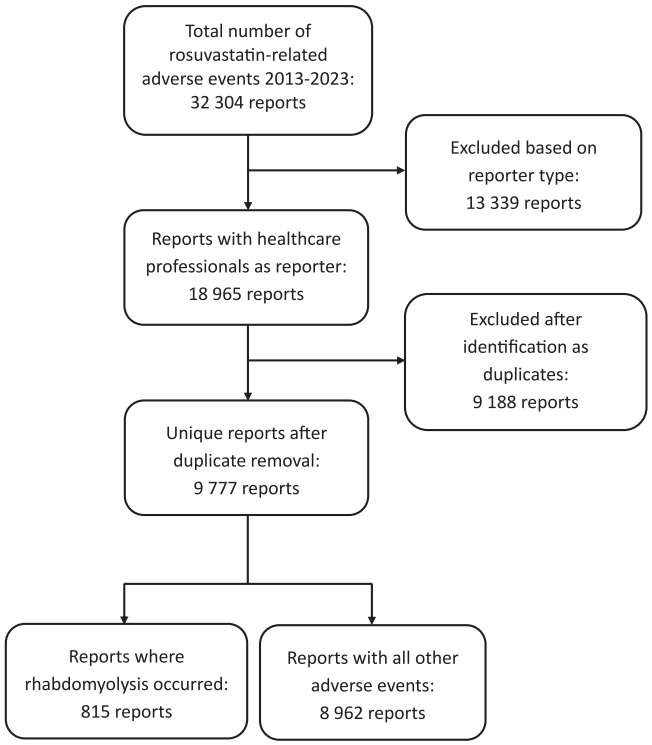

FIGURE 1 | Flow chart of the data handling process, illustrating the number of reports and applied exclusion criteria at each stage.

3 | Results

A total of 32 304 adverse event reports for rosuvastatin were retrieved from Q1 2013 to Q4 2023 from FAERS (Figure 1). After application of predefined selection criteria, a total of 18 965 adverse event reports were included in the study, and after duplicate removal, the remaining number of adverse event reports was 9777 reports. Rhabdomyolysis was reported as an adverse event in 8.3% (815/9777) of the reports. All other adverse events, except rhabdomyolysis, constituted 91.7% (8962/9777) of the reports. Baseline characteristics of the included patients are presented in Table 2.

Of the 71 BCRP inhibitors studied, only 36 had at least one (1) report in the interaction + rhabdomyolysis group (subgroup a). After exclusion of inhibitors with less than three reports in subgroup a, a total of 19 inhibitors remained for analysis (Table 3). In the initial analysis, interaction signals were statistically significant for amiodarone (ROR 1.63), erlotinib (ROR 44.2), febuxostat (ROR 2.47), rifampicin (ROR 4.25) and ticagrelor (ROR 4.15) (Table 3). It should be noted, however, that erlotinib had only one (1) report in subgroup b. Six other drugs (cyclosporine, dabigatran, felodipine, nilotinib, ritonavir and sildenafil) showed increased RORs (> 1), but, based on the CIs, they were not statistically significant.

The results of the adjusted analysis were consistent with the results of the initial analysis for all the significantly increased RORs (Table 4). ROR values slightly increased for erlotinib (ROR

TABLE 2 | Baseline characteristics of rhabdomyolysis reports and all other adverse events after data handling.

	Rhabdomyolysis present		Rhabdomyolysis absent		Total	
	n	**%**	***n***	**%**	***n***	**%**
Reports in group	815	8.3	8962	91.7	9777	100
Age range (years)		% of group		% of group		% of group
0–17	1	0.12	34	0.38	35	0.36
18–59	135	16.6	2265	25.3	2400	24.6
60–74	324	39.8	3167	35.3	3491	35.7
≥ 75	226	27.7	1511	16.9	1737	17.8
Not reported	129	15.8	1985	22.1	2114	21.6
Sex		% of group		% of group		% of group
Female	310	38.0	3971	44.3	4281	43.8
Male	454	55.7	4358	48.6	4812	49.2
Not reported	51	6.3	633	7.1	684	7.0

TABLE 3 | Initial ROR analysis of interaction signals for the concomitant use of rosuvastatin and drugs listed as strong BCRP inhibitors in vitro [10]. Only data of the 19 inhibitors with ≥ 3 reports in subgroup a are presented. ROR values for developing rhabdomyolysis were calculated according to the equation described in Section 2. An increased ROR value was considered statistically significant if the lower limit of the 95% CI exceeded 1 and subgroup a contained at least three reports.

Drug	a	b	c	d	ROR	95% CI lower	95% CI upper
Amiodarone	27	184	788	8778	1.63[a]	1.08	2.46
Apixaban	7	144	808	8818	0.53	0.25	1.14
Celecoxib	3	123	812	8839	0.27	0.08	0.84
Cyclosporine	7	39	808	8923	1.98	0.88	4.45
Dabigatran etexilate	6	60	809	8902	1.10	0.47	2.55
Erlotinib	4	1	811	8961	44.20[a]	4.93	395.91
Estradiol	3	47	812	8915	0.70	0.22	2.26
Febuxostat	14	63	801	8899	2.47[a]	1.38	4.43
Felodipine	6	45	809	8917	1.47	0.63	3.46
Fenofibrate	14	204	801	8758	0.75	0.43	1.30
Nifedipine	9	100	806	8862	0.99	0.50	1.96
Nilotinib	3	12	812	8950	2.76	0.78	9.78
Omeprazole	36	419	779	8543	0.94	0.67	1.33
Rifampicin	5	13	810	8949	4.25[a]	1.51	11.95
Ritonavir	4	28	811	8934	1.57	0.55	4.50
Sildenafil	4	32	811	8930	1.38	0.49	3.90
Telmisartan	12	158	803	8804	0.83	0.46	1.50
Ticagrelor	115	341	700	8621	4.15[a]	3.32	5.20
Vitamin D	38	498	777	8464	0.83	0.59	1.17

Note: a, interaction subgroup with rhabdomyolysis; b, interaction subgroup without rhabdomyolysis; c, non-interaction subgroup with rhabdomyolysis; d, non-interaction subgroup without rhabdomyolysis.
Abbreviations: CI, confidence interval; ROR, reporting odds ratio.
[a]Statistically significant ROR.

50.1) and rifampicin (ROR 5.22) when excluding reports containing the positive controls febuxostat and ticagrelor from the analysis. Likewise, the ROR of febuxostat increased to 2.57 when removing ticagrelor reports, and that of ticagrelor increased to 4.16 after removal of febuxostat reports. Seven compounds (cyclosporine, dabigatran, felodipine, nifedipine, nilotinib, ritonavir and sildenafil) showed RORs above 1, but they were not statistically significant.

4 | Discussion

In this study, potential DDI signals between rosuvastatin, a widely used statin and a known BCRP substrate, and drugs listed as strong inhibitors of BCRP in vitro were evaluated through analysis of adverse event data from the FAERS database. The primary objective was to investigate the association between concomitant drug use and rhabdomyolysis, a rare but serious and potentially fatal adverse effect associated with statin therapy. Of the 71 inhibitors studied, 19 drugs had enough reports for analysis. Significantly increased RORs were observed for the clinically established BCRP inhibitors ticagrelor and febuxostat. Additionally, three other BCRP inhibitors (amiodarone, erlotinib and rifampicin) exhibited significantly increased RORs for rhabdomyolysis, whereas six inhibitors (cyclosporine, dabigatran, felodipine, nilotinib, ritonavir and sildenafil) showed elevated RORs that did not reach statistical significance.

Ticagrelor demonstrated a significantly increased ROR (4.15) for rhabdomyolysis when co-administered with rosuvastatin. Several studies have reported cases of rhabdomyolysis associated with the concomitant use of ticagrelor and rosuvastatin [12–15]. Lehtisalo et al. [5] carried out a clinical study in healthy volunteers, where ticagrelor increased rosuvastatin AUC by almost threefold and suggested inhibition of BCRP-mediated efflux of rosuvastatin in the intestine as the cause of the observed interaction. The findings of the present real-world data-based study are in line with these previous observations and support an increased risk of rhabdomyolysis with the co-administration of ticagrelor and rosuvastatin.

TABLE 4 | Adjusted ROR analysis of interaction signals for the concomitant use of rosuvastatin and drugs listed as strong BCRP inhibitors in vitro [10]. Reports with the positive controls febuxostat and ticagrelor have been excluded, as described in Section 2. Only data of the 19 inhibitors with ≥3 reports in subgroup a is presented. ROR values for developing rhabdomyolysis were calculated according to the equation described in Section 2. An increased ROR value was considered statistically significant if the lower limit of the 95% CI exceeded 1 and subgroup a contained at least three reports.

Drug	a	b	c	d	ROR	95% CI lower	95% CI upper
Amiodarone	22	172	665	8386	1.61[a]	1.03	2.53
Apixaban	7	140	680	8418	0.62	0.29	1.33
Celecoxib	3	122	684	8436	0.30	0.10	0.96
Cyclosporine	5	39	682	8519	1.60	0.63	4.08
Dabigatran etexilate	6	59	681	8499	1.27	0.55	2.95
Erlotinib	4	1	683	8557	50.11[a]	5.59	449.01
Estradiol	1	45	686	8513	0.28	0.04	2.00
Febuxostat	13	63	687	8558	2.57[a]	1.41	4.69
Felodipine	6	44	681	8514	1.70	0.72	4.01
Fenofibrate	14	198	673	8360	0.88	0.51	1.52
Nifedipine	8	87	679	8471	1.15	0.55	2.38
Nilotinib	3	12	684	8546	3.12	0.88	11.10
Omeprazole	21	387	666	8171	0.67	0.43	1.04
Rifampicin	5	12	682	8546	5.22[a]	1.83	14.86
Ritonavir	4	28	683	8530	1.78	0.62	5.10
Sildenafil	4	32	683	8526	1.56	0.55	4.43
Telmisartan	11	144	676	8414	0.95	0.51	1.76
Ticagrelor	114	341	687	8558	4.16[a]	3.32	5.22
Vitamin D	34	481	653	8077	0.87	0.61	1.25

Note: a, interaction subgroup with rhabdomyolysis; b, interaction subgroup without rhabdomyolysis; c, non-interaction subgroup with rhabdomyolysis; d, non-interaction subgroup without rhabdomyolysis.
Abbreviations: CI, confidence interval; ROR, reporting odds ratio.
[a]Statistically significant ROR.

Like ticagrelor, febuxostat is also a known inhibitor of BCRP and has increased rosuvastatin AUC by twofold in healthy volunteers [6]. At least one case report of rhabdomyolysis associated with the combined use of febuxostat and rosuvastatin has been published, in which colchicine was also co-administered [17]. Three other cases of rhabdomyolysis have been published for febuxostat, two of them in combination with other drugs and one in monotherapy [18–20]. Mitsuboshi and Kotake [21] conducted a disproportionality analysis using FAERS and a meta-analysis of randomized controlled trials to evaluate the risk of muscle injury associated with febuxostat. Whereas their FAERS analysis revealed a statistically significant association for rhabdomyolysis, the meta-analysis did not demonstrate a significantly increased muscle injury risk compared to placebo or allopurinol. Taken together, although our data demonstrate an increased ROR (2.5) for rhabdomyolysis with concomitant use of febuxostat and rosuvastatin, this finding is not necessarily solely due to febuxostat-mediated BCRP inhibition, as both drugs independently could increase the risk of rhabdomyolysis.

Several case reports have described rhabdomyolysis occurring in patients using amiodarone and rosuvastatin concomitantly [14, 22, 23]. However, all these reported cases involve other concomitant drugs, in two cases ticagrelor, making it difficult to isolate the contribution of the amiodarone–rosuvastatin combination. Accordingly, our study design does not allow assessment of whether this interaction could be the primary causative factor. To our knowledge, no studies have explicitly attributed rhabdomyolysis to this combination alone. Although amiodarone inhibits BCRP in vitro [10], its clinical relevance is unknown. On the other hand, the increased ROR (1.6) of amiodarone in our study remained statistically significant also in the adjusted analysis, indicating that reports including clinically relevant BCRP inhibitors did not act as a confounding factor for the result.

Previous studies have identified erlotinib as an inhibitor of BCRP in vitro [10, 24]. In a Phase I open-label study in cancer patients, co-administration of standard dose erlotinib with high-dose rosuvastatin markedly increased the myalgia rate, and one case of fatal rhabdomyolysis occurred during the study [25]. The study

did not, however, investigate the effect of erlotinib on rosuvastatin plasma concentrations. Nevertheless, very high rosuvastatin doses were used in the study (1–2 mg/kg/day) exceeding the highest recommended dose for hypercholesterolaemia, 40 mg/day. These elevated doses could independently increase the risk of rosuvastatin-induced muscle toxicity. Although the study by Goss et al. [25] appears to be the only published report specifically linking concomitant use of erlotinib and rosuvastatin to rhabdomyolysis, the summary of product characteristics of Tarceva (original erlotinib product) includes a warning for myopathy, including rhabdomyolysis, when used in combination with statins [26]. It does not, however, specifically mention BCRP or rosuvastatin. The high DDI signal for erlotinib (ROR 44) obtained in our study should be interpreted with caution. It was derived from a small number of reports ($n = 4$ in subgroup a, $n = 1$ in subgroup b) and may also be the result of residual confounding related to oncology populations and frequent polypharmacy.

Rifampicin inhibits BCRP in vitro [10, 27], as well as OATP1B1 and OATP1B3 [28]. A single oral dose of rifampicin has been reported to increase rosuvastatin AUC by two- to fourfold in healthy volunteers [29–31]. In contrast, a dose-dependent decrease in rosuvastatin AUC has been observed following multiple-dose rifampicin administration in healthy volunteers, with the AUC decreasing approximately by 60% after 10 days of rifampicin 600 mg daily [32]. The observed DDI after repeated rifampicin dosing has been suggested to involve induction of OATPs and cytochrome P450 2C9. Thus, these previous studies indicate that rifampicin might act as an inhibitor after a single dose and as an inducer after multiple doses, but the mechanisms are not well understood. Notably, in the multiple-dose study [32], rifampicin was apparently administered several hours before rosuvastatin. Therefore, any potential inhibitory effect of rifampicin, particularly on gut BCRP, had likely subsided before rosuvastatin administration. Consequently, the net effect of rifampicin's inhibition and induction on rosuvastatin concentrations is highly context dependent and may vary depending on the number of rifampicin doses and the timing of its administration relative to rosuvastatin. In the present study, an increased ROR (4.3) was observed for the combination of rifampicin and rosuvastatin. We are, however, not aware of any case reports of rhabdomyolysis due to concomitant use of rifampicin and rosuvastatin.

In the present study, only 19 of the 71 BCRP inhibitors included had a sufficient number of reports in subgroup a for analysis (Table S1). Of these inhibitors, 14 did not show a statistically significant increase in ROR. The absence of a sufficient number of reports or a significant ROR increase does not necessarily rule out a clinically relevant interaction. Factors such as the likelihood of concomitant exposure to two drugs in clinical practice may influence the detection of a signal. If a BCRP inhibitor is used only occasionally, such as sildenafil or vitamin D, a potential interaction may remain undetected. On the other hand, the clinical importance of such DDIs might also be limited. Clinical awareness of DDIs might also affect signal detection. For instance, cyclosporine showed an increased ROR (1.98) that did not reach statistical significance. It has, however, been shown to increase rosuvastatin AUC and peak plasma concentration in heart transplant patients on cyclosporine therapy by 7-fold and 11-fold, respectively, compared to healthy volunteers not taking cyclosporine [33]. Initial in vitro studies suggested an OATP1B1-mediated DDI [33], with later studies indicating that cyclosporine additionally inhibits OATP1B3 [34] and BCRP [35]. One case report has linked rhabdomyolysis in a kidney transplant recipient to the concomitant use of cyclosporine and rosuvastatin [36]. The lack of a significant signal in the present study may reflect clinical awareness of the interaction and subsequent dose adjustments.

Conversely, a significantly increased ROR for rhabdomyolysis with a specific drug combination does not necessarily imply a causal DDI. Furthermore, an increased ROR cannot be conclusively attributed to the specific drug combination alone. Confounding factors, such as underlying medical conditions, diseases and genetics or the use of other concomitant drugs, can affect the results, as they cannot be taken into consideration using this method. In particular, variants of *ABCG2* and *SLCO1B1*, the genes coding for BCRP and OATP1B1, respectively, may affect rosuvastatin concentrations and hence the outcome observed in these data. Further studies are required to characterize whether the observed associations in the present study reflect pharmacokinetic DDIs and, if so, to determine whether these are mediated by BCRP inhibition or some other mechanism, for example, overlapping inhibition of several transporters. At least, erlotinib and rifampicin have shown in vitro inhibition of other drug transporters that are involved in rosuvastatin pharmacokinetics [28, 37]. Also, changes in inhibitor exposure and site of inhibition affect the outcome of the interaction.

Like other studies utilizing pharmacovigilance databases, this study has limitations related to the reports themselves. The spontaneous reporting system database can be subject to various types of bias and confounding [38]. For instance, the system may contain reports with incomplete information and high numbers of duplicate reports. Although a strict predefined protocol was implemented in this study to mitigate bias due to duplicates, the process was complicated by the incompleteness of the reports. In cases where suspected duplicates provided complementary information, reports were merged to maximize data completeness while minimizing redundancy. In this study, we restricted the analysis to reports submitted by healthcare professionals to improve the clinical reliability of rhabdomyolysis diagnoses. This approach may have affected signal sensitivity and introduced reporting bias. Specifically, excluding non–healthcare professional reports may have reduced the total number of cases captured and potentially limited the detection of weaker signals. Other general limitations of database-based studies are underreporting and changes in reporting frequencies over time [38], which could potentially hide or mask the true frequency of the studied event. This is especially relevant for rare events like rhabdomyolysis, where a small number of reports could significantly influence signal detection.

In this study, rhabdomyolysis was selected as the adverse event of interest, as it has been previously associated with the concomitant use of the clinically known BCRP inhibitor ticagrelor and rosuvastatin [12–15, 17–20]. As a concentration-dependent adverse event, rhabdomyolysis may arise from interactions that increase rosuvastatin exposure. In contrast to milder forms of myalgia, rhabdomyolysis is clinically confirmed and typically supported by objective laboratory data (such as creatine kinase

levels), which minimizes confounding by subjective symptom reporting.

Our findings for the positive controls febuxostat and ticagrelor are in line with previous studies and support the robustness of the analytical methodology. Also, our results for the other inhibitors with significantly increased RORs seem to be robust. After excluding reports with febuxostat and ticagrelor, their adjusted RORs remained largely consistent with the initial analysis. This finding indicates that the observed associations are not driven by confounding from ticagrelor or febuxostat. Although other confounding factors might still influence the results, the adjusted analysis strengthens the validity of our findings.

To conclude, this study supports previous findings on an association between clinically known BCRP inhibitors ticagrelor and febuxostat and an increased risk of rosuvastatin-induced rhabdomyolysis. Additionally, the study suggests that amiodarone, erlotinib and rifampicin may be associated with an increased risk of rhabdomyolysis when used concomitantly with rosuvastatin. Further studies are needed to validate these signals and to characterize the underlying mechanisms of the potential DDIs and their role in rosuvastatin-associated rhabdomyolysis. Finally, this study emphasizes the utility of pharmacovigilance data in detecting DDI signals.

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Ethics Statement

Ethical approval was not required for this study because it was based exclusively on publicly available, de-identified data from the FDA Adverse Event Reporting System (FAERS).

Conflicts of Interest

Ronja Levomäki is currently employed by Biocodex. The other authors declare no conflicts of interest.

Data Availability Statement

Data available on request from the authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Drugs listed as strong BCRP-inhibitors in vitro (Deng et al. 2023) and investigated as inhibitors in the current study.