

## Research Article

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# Potential drug interactions with statins: Estonian register-based study

**Abstract:** In Estonia, HMG-CoA reductase inhibitors are widely used to modify lipid levels but there are no current data on additional medicines prescribed alongside the statins. The aim of this study was to identify the frequency of potential clinically relevant interactions at a national level among an outpatient population treated with statins between January and June 2008, based on the prescription database of the Estonian Health Insurance Fund. This retrospective prevalence study included 203,646 outpatients aged 50 years or older, of whom 29,367 received statin therapy. The study analysed individuals who had used at least one prescription medicine for a minimum of 7 days concomitantly with statins. Potential drug interactions were analysed using Epocrates online, Stockley's Drug Interactions, and the drug interaction database developed in Estonia. Statins metabolised by the CYP3A4 isoenzyme were prescribed to 64% of all statin users. Medicines known to have potentially clinically significant interactions with statins were prescribed to 4.6% of patients.

The drugs prescribed concomitantly most often with simvastatin were warfarin (5.7%) and amiodarone (3.9%), whereas digoxin (1.2%) and ethinylestradiol (2%) were prescribed with atorvastatin.

Potential interactions were not detected in the treatment regimens of rosuvastatin, pravastatin, and fluvastatin users.

**Keywords:** HMG-CoA reductase inhibitors (statins), drug-drug interactions

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## 1 Introduction

Mortality and morbidity due to cardiovascular diseases with an atherosclerotic genesis are a major public health issue. Lipid-lowering medicines and in particular, HMG-CoA reductase inhibitors (statins), are commonly used to reduce the risk of negative cardiovascular outcomes [1-4]. Clinical studies have proven the efficacy and safety of statins in the treatment of these diseases [1-4]. However, problems associated with adverse drug reactions (ADRs) have emerged as the use of these medicines becomes more widespread. The most common ADRs include symptoms in the muscular system, which extend from mild muscle pain to rhabdomyolysis and elevated transaminases [4]. Statin-induced myopathy occurs in 1.5-3.0% of clinical trial participants, whereas rates range widely from 0.3% to 33% in routine clinical practice [4,5,6,7].

The risk of HMG-CoA reductase inhibitor-related ADRs increases significantly with the concomitant prescription of interacting medicines [8]. Approximately 60% of the cases of statin-related rhabdomyolysis relate to drug interactions [4]. The mechanism underlying most statin drug interactions involves the cytochrome P450 (CYP) system [6]. Simvastatin and atorvastatin are metabolised by the CYP3A4 enzyme and fluvastatin primarily by CYP2C9 [7]. Pravastatin and rosuvastatin undergo minimal metabolism by the CYP enzymes [6]. Potentially dangerous interactions in simvastatin and atorvastatin users have been reported where there is concomitant use of CYP3A4 inhibitors: drug concentrations may increase and there is a

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risk of toxicity [9]. Several drugs commonly used by middle-aged or older people, such as omeprazole, macrolide antibacterials, and cardiovascular drugs including warfarin, may precipitate statin-induced myopathy [8,10-12]. Older dyslipidaemic patients are at a higher risk of clinically relevant potential drug-drug interactions primarily due to the higher number of drugs used [13].

A recent nationwide study by Bakhai et al. demonstrated that the co-prescription of CYP3A4-metabolised statins and CYP3A4 inhibitors is common in UK primary care [14]. According to the statistics of the Estonian State Agency of Medicines, the usage of statins metabolized by the CYP system is also frequent; however, there are no studies on potential drug interactions with CYP inhibitors and other drugs [15].

The aim of this study was to examine the incidence of potential clinically relevant interactions among users of HMG-CoA reductase inhibitors at a national level in Estonia.

## 2 Material and methods

### 2.1 Study sample

For this retrospective registry-based study, data from the prescription database of the Estonian Health Insurance Fund was used. All identification data acquired from the Estonian Health Insurance Fund were coded.

The study population included individuals aged 50 years or older with at least two prescriptions during the study period (from January 1 until June 30, 2008). The number of patients included in the database was 203,646, comprising 43.1% of the Estonian population aged 50 and over. Patients ( $n=29,367$ ) who were prescribed statin therapy were further identified. In 600 patients, one statin was replaced with another during the study period (atorvastatin and rosuvastatin were replaced with simvastatin), and these patients were regarded as users of simvastatin for the analyses (Figure 1).

### 2.2 Data analyses

Initiation of statin therapy was determined based on the purchase date of the medicine, and the duration of therapy was defined as the number of defined daily doses (DDDs).

The prescription medicines used concomitantly with statins were identified, and the average number of these medicines based on different age and gender groups was analysed. Potential interactions with statins as identified using the national drug interaction database KIS (“Koostoimeteinfosüsteem” in Estonian) were determined.

This database, developed by Uibokand and Zharkovsky, is currently being used as an instrument for the detection of potential interactions in prescription schemes at community pharmacies in Estonia [16]. This national database evaluates the potential interactions of multiple pharmaceuticals. It uses a risk-rating classification of interactions based on previously published criteria, outlines the possible clinical manifestation of the interaction and provides recommendations for further action (e.g., concomitant use of specific medicine pairs should be avoided or that certain clinical parameters should be monitored) [17].

The data obtained on potential interactions were further verified using two additional interaction databases: Epocrates online and Stockley’s Drug Interactions [18,19]. Epocrates online is a database widely used by physicians, and based on current literature, it demonstrates a high level of validity [20].

Statistical analyses were performed using SAS software. The mean standard deviation (SD) was calculated, and comparisons were made using Tukey’s test. Linear correlation coefficients and Pearson’s correlation coefficients were calculated.

This study was approved by the Ethics Review Committee (ERC) on Human Research of the University of Tartu.

## 3 Results

Of the 203,646 patients in the database, 29,367 (10,768 men and 18,599 women) received statin treatment during the first half of 2008. Statins metabolised by the CYP3A4 enzyme were prescribed to 64% of all patients undergoing statin treatment (Table 1). The mean number of concomitant medicines prescribed to patients receiving statin therapy was 4.4 (SD=1.9) and ranged from 2 to 18 (Table 2).

Medicines potentially interacting with statins were prescribed to 1,354 patients (4.6% of all patients who received statin treatment); 1,256 patients (4.3%) received medicines that potentially interacted with simvastatin, and 98 patients (0.3%) received medicines that potentially interacted with atorvastatin.

**Table 1:** Mean age of users of different statins

Statin	Mean age (SD)		Mean age of all patients (SD) n-number of patients (% of all statin users)
	Male n-number of patients	Female n-number of patients	
Simvastatin*	69.65 (8.3) n=4978	65.98 (8.6) n=7835	68.2 (8.6) n=12,816 (43.6)
Atorvastatin	65.1 (8.4) n=2074	68.0 (8.3) n=3818	67.0 (8.5) n=5892 (20%)
Fluvastatin	64.5 (8.5) n=307	67.9 (8.3) n=513	66.7 (8.6) n=820 (2.7%)
Pravastatin	67.4 (8.2) n=785	70.5 (8.1) n=1064	69.2 (8.3) n=1849 (6.2%)
Rosuvastatin	62.5 (8.2) n=3061	65.9 (8.4) n=5518	64.7 (8.5) n=8579 (29%)
All statin users	n=10,768	n=18,599	67.0 (8.7) n=29,367 (100%)

\* chi-square test  $p < 0.05$

**Table 2:** Mean number of medicines and potential interactions among statin users by age and gender.

	Age				Total N=29,367
	50-60 N=7922	61-70 N=11,085	71-80 N=8802	80+ N=1558	
All patients					
Number of drugs (SD)	4.09(1.83)*	4.34(1.93)	4.65(1.94)	4.78(1.9)	4.41(1.92)
Number of potential interactions (SD)	0.04(0.27)*	0.06(0.35)	0.07(0.38)	0.06(0.33)	0.06(0.34)
Male	3730	3952	2649	437	10,768
Number of drugs (SD)	4.52(2.14)	4.98(2.41)	5.23(2.38)	5.56(2.52)	4.05(1.86)
Number of potential interactions (SD)	0.05(0.31)	0.1(0.46)	0.12(0.53)	0.08(0.38)	0.09(0.43)
Female	4192	7133	6153	1121	18,599
Number of drugs (SD)	4.47(2.37)	4.85(2.46)	5.32(2.54)	5.4(2.36)	3.96(1.89)
Number of potential interactions (SD)	0.03(0.23)	0.04(0.26)	0.05(0.31)	0.06(0.31)	0.04(0.27)

\* $p < 0.05$  as compared with other age groups (Tukey test)

The most commonly prescribed medicines (detailed description of interaction mechanisms is provided in Tables 3 and 4) that could potentially interact with simvastatin were warfarin (n=729), amiodarone (n=505), ketoconazole (n=11), cyclosporine (n=7), and itraconazole (n=4; Table 3). More than one potential interaction with statins could have occurred in 23 patients (men = 16, women = 7). In these patients, simvastatin was used with warfarin and amiodarone.

The medicines that could potentially interact with atorvastatin were digoxin (n=69), claritromycin (n=10),

erythromycin (n=4), itraconazole (n=3), and ethinylestradiol (n=12; Table 4).

No potentially interacting medicines were prescribed to the patients who received rosuvastatin, pravastatin and fluvastatin treatment.

Age-group comparisons (Chi-squared test  $p < 0.05$ ) showed that the patients receiving rosuvastatin were younger than those receiving simvastatin (Table 1). Simvastatin was primarily used in the 61-70-year age group. This age group was characterised by the highest number of users of potentially interacting medicines (e.g.,

**Table 3:** Interaction details of simvastatin with other medicines

Number of cases (% of simvastatin users)	Concomitant medicine	Potential adverse reactions	Mechanism of interaction	References
729 (5.7)	Warfarin	Anticoagulant effect of warfarin may be potentiated	Deceleration of warfarin metabolism due to CYP3A4 enzyme inhibition	16,17,18,23
505 (3.9)	Amiodarone	Increased risk of rhabdomyolysis	Inhibition of CYP enzymes resulting in the decreased metabolic clearance of simvastatin	6,11,12,16,17,18,22
11 (<0.1)	Ketoconazole	Increased risk of rhabdomyolysis	Inhibition of CYP enzymes	6,16,17,18
7 (<0.1)	Cyclosporine	Increased risk of rhabdomyolysis	Mechanism unknown, possible deceleration of simvastatin metabolism due to CYP3A4 enzyme inhibition	6,16,17,18
4 (<0.1)	Itraconazole	Increased risk of rhabdomyolysis	Inhibition of CYP enzymes	6,9,16,17,18,26

**Table 4:** Interaction details of atorvastatin with other medicines

Number of cases (% of atorvastatin users)	Concomitant medicine	Potential adverse reactions	Mechanism of interaction	References
69 (1.2)	Digoxin	Digoxin plasma levels might increase	Inhibition of CYP enzymes	16,17,18
12 (0.2)	Ethinylestradiol	Ethinylestradiol levels might increase	Inhibition of CYP enzymes	16,17,18
10 (<0.1)	Clarithromycin	Increase risk of rhabdomyolysis	Inhibition of CYP enzymes	6,9,16,17,18,26
4 (<0.1)	Erythromycin	Increase risk of rhabdomyolysis	Inhibition of CYP enzymes	6,9,16,17,18,26
3 (<0.1)	Itraconazole	Increase risk of rhabdomyolysis	Inhibition of CYP enzymes	6,9,16,17,18,26

warfarin and amiodarone). In patients over 60 years of age, simvastatin was used in doses of 10 mg (19.2%), 20 mg (73.8%), 40 mg (7%), and 80 mg (0.01%). This pattern of doses is similar to that of the younger patient group (50-60 years).

There were no differences in concurrently used medicines between men and women (4.4, SD=1.9 in both); however, potential interactions were more frequent among men (0.09, SD=0.4) than women (0.04, SD=0.3), and this difference was statistically significant ( $p < 0.001$ ).

There was a correlation between potential interactions and the number of concomitant medicines ( $p < 0.001$ ) and between age and potential interaction ( $p < 0.03$ ). As

the number of concomitantly used medicines and age increase, the frequency of potential drug interactions may increase.

Logistic regression analysis based on the reference group for the population in the 50-60-year group range demonstrated that the odds of exposure to potential interactions among statin users was highest in the 61-70 age group (OR 1.23; 95% CI 1.23; 1.75).

The odds of exposure were higher among men than women (OR 2.09; 95% CI 1.8; 2.37). Moreover, the odds of exposure were higher among simvastatin users than atorvastatin users (OR 1.67; 95% CI 1.44; 1.94).

## 4 Discussion

This is the first study evaluating potential drug-drug interactions of statins with concomitantly prescribed medicines among the older population in Estonia.

In our nationwide study, 29,367 patients used HMG-CoA reductase inhibitors. Within this cohort, 64% patients received statins (simvastatin or atorvastatin), which are metabolised by the CYP3A4 enzyme; however, only 5% of the patients who used simvastatin or atorvastatin were at a risk of potentially clinically relevant interactions.

In our study, the percentage of patients receiving potentially interacting medicines with simvastatin is consistent with results from a previous study published by Rätz Bravo et al. [20]. In that study, 12% of simvastatin users were prescribed with potentially interacting drugs in their treatment schemes [20]. In our study, potentially interacting drugs were prescribed in 10% of simvastatin users. It should be noted however, that in the study of Rätz Bravo [20], simvastatin users constituted 28%, whereas in our study, 44% of all patients received statin treatment.

Much higher prevalences have been reported in the UK where 93% of patients used statins metabolised by the CYP3A4 enzyme. and every third patient concomitantly

took medicines that inhibited the metabolism of statins [21]. Previous studies showed that a combination of simvastatin with fibrates, cyclosporine, digoxin, macrolide antibiotics, warfarin or azoles increased the risk of statin-mediated rhabdomyolysis [9,22,23]. Therefore, in our study, 10% of simvastatin users (4.3% of all statin users) are at a risk of developing rhabdomyolysis. Furthermore, if warfarin and simvastatin are used concomitantly (729 patients in our study), an increased risk of haemorrhage should also be highlighted alongside the increased risk of rhabdomyolysis [23,24].

Data analysis showed that in 600 patients (2%), the safe and less interactive atorvastatin and rosuvastatin were replaced by the highly interacting simvastatin (Figure 1).

Here, the cost of the medicines may have been the reason for the change – more expensive medicines were replaced with cheaper analogues without consideration of the potential risks due to drug interactions, which may become clinically significant, especially in the older population and in particular, in the case of polypharmacy [10, 22].

In our study, potentially interacting medicines were prescribed to only 0.6% of patients using atorvastatin.

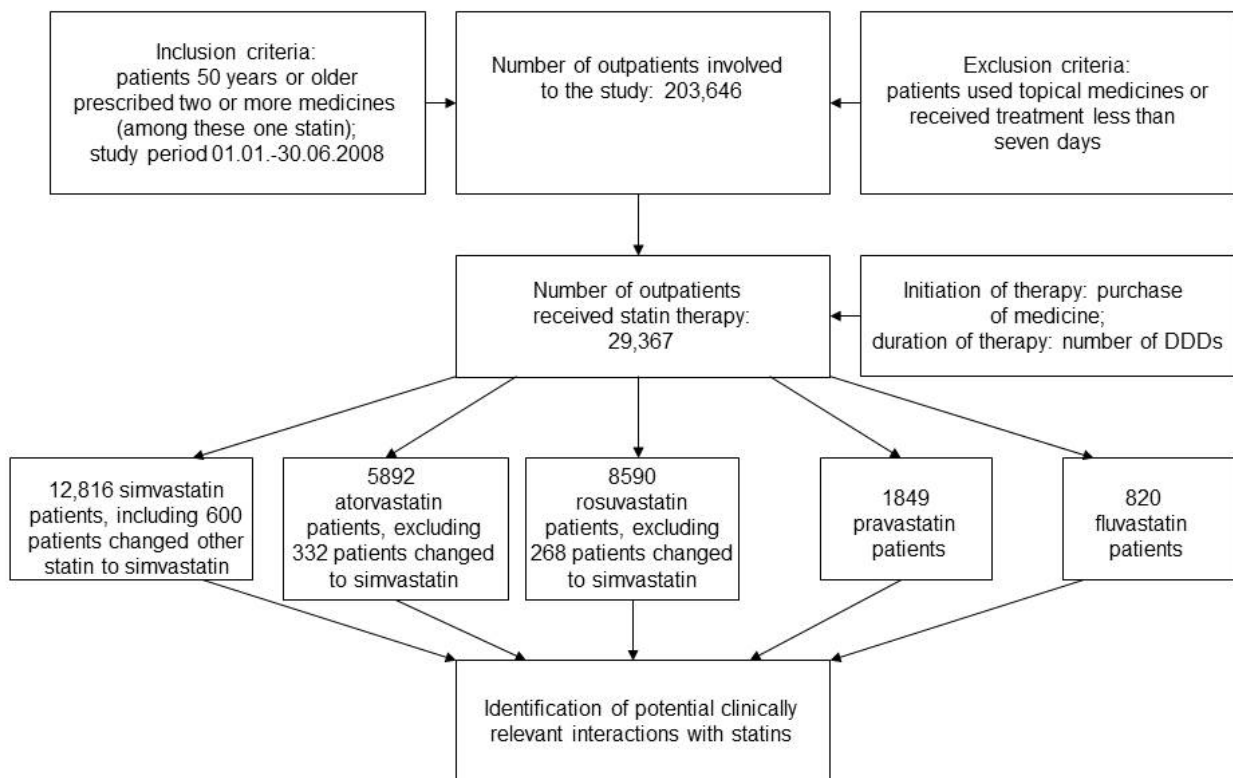


Figure 1: The study protocol and study sample

Atorvastatin was combined with digoxin (0.2%) and ethinylestradiol (<0.1%), clarithromycin (<0.1%), erythromycin (<0.1%), and itraconazole (<0.1%). The atorvastatin-digoxin interaction should be highlighted separately because there is a danger of an atorvastatin-mediated increase in digoxin concentrations [25]. Atorvastatin metabolism is less affected by the inhibition of the CYP 3A4 enzyme; therefore, potential interactions are clinically less important [6]. Furthermore, patients were prescribed small doses of atorvastatin (10 and 20 mg); thus, the likelihood of an interaction is small.

Potential interactions were not found in treatment regimens including rosuvastatin or in pravastatin or fluvastatin users. Fluvastatin is metabolised via CYP2C9, and potential interactions are rarely found. CYP enzymes do not contribute to the metabolism of pravastatin and rosuvastatin [8,26].

The main limitation of this study is the fact that there is no information available on whether the interactions manifested clinically when the potentially interacting medicines were used. There are data in the literature that suggest that myopathy occurs more often in patients using statins with CYP3A4 inhibitors [4,6,8]. In our study, only 10 patients used clarithromycin with atorvastatin; therefore, the percentage of these patients is very low.

## 5 Conclusions

This study revealed that a high number of potential interactions may occur in patients using simvastatin in comparison with other statins. This finding suggests a real safety issue among the older population. Statin prescription should be based on clinical rather than economic considerations, and statins with a lower likelihood of interactions should be administered, preferably to elderly patients who are receiving polypharmacotherapy.

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### Author contributions:

Maia Gavronski – concept/design, data collection, statistics, data analysis/interpretation and drafting the article

Daisy Volmer – critical revision of the article.

Sirpa Hartikainen – critical revision of the article

Alexander Zharkovsky – concept/design and critical revision of the article

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