

# The Relationship Between Suspected Adverse Drug Reactions Of HMG-Coa Reductase Inhibitors And Polypharmacology Using A National Registry Approach

Yousaf, Hasan; Jones, Alan M

DOI:

[10.1101/2024.04.02.24305224](https://doi.org/10.1101/2024.04.02.24305224)

License:

Creative Commons: Attribution (CC BY)

*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Yousaf, H & Jones, AM 2024 'The Relationship Between Suspected Adverse Drug Reactions Of HMG-Coa Reductase Inhibitors And Polypharmacology Using A National Registry Approach' medRxiv.  
<https://doi.org/10.1101/2024.04.02.24305224>

[Link to publication on Research at Birmingham portal](#)

## General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

## The Relationship Between Suspected Adverse Drug Reactions Of HMG-Coa Reductase Inhibitors And Polypharmacology Using A National Registry Approach

Hasan Yousaf,<sup>1</sup> Alan M. Jones<sup>1\*</sup>

<sup>1</sup>Medicines Safety Research Group, School of Pharmacy, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom.

### Abstract

#### *Aims*

The aim of this study was to explore the suspected adverse drug reaction (ADR) data of five licensed statins in the UK: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin. A secondary aim was to determine if there was a link between the polypharmacological properties of the statins and their associated muscle-related side effects.

#### *Methods*

The chemical database of bioactive molecules with drug-like properties, European Molecular Biology Laboratory (ChEMBL) was used to obtain data on the pharmacological interactions of statins with human proteins. The Medicines and Healthcare products Regulatory Agency's (MHRA) Yellow Card Scheme was used to obtain reports of suspected ADRs from 2018 to 2022. The OpenPrescribing database was used to obtain the prescribing rates for statistical interpretation.

#### *Results*

The study found no significant difference between the statins in causing ADRs across all organ classes ( $X^2$ ,  $P > .05$ ). Fluvastatin was found to have a higher incidence of ADRs/100,000  $R_x$  across multiple organ classes.

#### *Conclusion*

No significant difference was found between the suspected ADR incidence of the statins across all organ classes. No evidence of higher intensity statins causing more muscle symptoms than moderate intensity statins was found.

### Keywords

Statins; Adverse drug reaction; pharmacovigilance; clinical pharmacology; Yellow Card

## Introduction

Statins are a group of lipid-lowering drugs that act by inhibiting 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A reductase, the rate-limiting enzyme for the synthesis of mevalonic acid from HMG-coenzyme A.[1] Mevalonic acid is converted *via* precursor molecules into cholesterol. By inhibiting cholesterol synthesis, the body upregulates low-density lipoprotein (LDL) receptors causing a decrease in plasma LDL-cholesterol.[2] Elevated LDL-cholesterol is associated with an increased risk of myocardial infarction (MI) and atherosclerotic cardiovascular disease (CVD), which further increases with age.[3-4] Statins are proven to reduce plasma LDL-cholesterol and mortality including in the Scandinavian Simvastatin Survival Study (4S), where simvastatin caused a 35% mean reduction in plasma LDL and 30% reduction in fatal outcomes compared to placebo. [5] Statins have also proved to be effective in multiple large-scale trials.[6] This study will focus on five statins licensed in the United Kingdom: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin.[7]

An adverse drug reaction (ADR) is an unintended harmful reaction to the use of a drug.[8] The degree of harm may range from a mild effect through to permanent or fatal outcomes. Statins like all drugs have their own unique ADRs: muscle related ADRs concurrent with statin prescribing such as muscle pain (myalgia) being the most reported ADR.[9]

Mechanisms have been proposed for statin-induced myopathy however there is no singular agreed pathway. A mechanism involving the dissociation of the FKBP12 binding protein, from sarcoplasmic reticulum  $Ca^{2+}$  channels in myocytes, causing pro-apoptotic signalling; but these effects were also present in patients who had not experienced myalgia so may only affect individuals susceptible due to genetics /other factors.[10-11] Higher intensity statins which cause a  $\geq 50\%$  reduction in LDL-cholesterol[12] have been associated with increased risk of myopathy, which also brings the pharmacokinetic parameters of the statins into consideration.[13-14]

We herein report an approach to identifying patterns between the statin structures, their unique pharmacology and suspected ADR signals.[15-19]

## Aims

The primary aim of this research is to explore suspected ADR data of atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin using a national registry approach. A secondary aim is to determine whether there is a link between the physicochemical and pharmacological properties of these statins and their associated side effects.

## Methods

### *Chemical properties and pharmacology*

The chemical database of bioactive molecules with drug-like properties, European Molecular Biology Laboratory (ChEMBL)[20] and Electronic Medicines Compendium (EMC)[21] were used to obtain the physicochemical properties and pharmacokinetic parameters for atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin.

Physicochemical properties included  $pK_a$ ,  $cLog_{10}P$ ,  $cLog_{10}D_{7.4}$ , topological polar surface area ( $tPSA$ ) and the number of hydrogen bond donors (HBD) and acceptors (HBA). Certain properties increase the propensity of a molecule to penetrate the blood brain barrier (BBB)[22-23] as follows: a molecular weight of  $<450$  Da, a neutral or basic drug molecule, the molecule not being a substrate of P-glycoprotein,  $<6$  HBD and  $<2$  HBA, a  $tPSA$  of  $<90 \text{ \AA}^2$  and a  $log_{10}D$  of 1-3 at  $pH = 7.4$ . Penetration of the BBB can lead to potential neurological side effects.

Lipophilic ligand efficiency (LLE) was calculated where  $LLE = pIC_{50} - cLog_{10}P$ .  $pIC_{50}$  is the negative  $log_{10}$  of the  $IC_{50}$ , which is the concentration of drug needed to inhibit 50% of the activity of a process or response at a receptor; median  $IC_{50}$  values for each statin acting on HMG-CoA reductase were used.  $cLog_{10}P$  is the calculated partition coefficient of a substance in its neutral form between an aqueous and organic phase. The LLE is a measure

of the specificity of a molecule for its target accounting for its partitioning in the organic phase.[24] An LLE of  $>5$  is associated with a significantly smaller risk of toxicity.[25]

Pharmacokinetic properties were obtained from the EMC and included the bioavailability, half-life, CYP450 activity and the degree of plasma protein binding. Experimental  $C_{max}$  values were obtained from literature databases by searching the drug name and  $C_{max}$ . [26-30] The volume of distribution was obtained from the EMC, Drugbank,[31] and from a trial for simvastatin.[32] Literature searches also determined if the statins were P-glycoprotein substrates.[33]

#### *Pharmacological interactions*

The ChEMBL database was used to identify interactions between each statin and *homo sapien* proteins/targets. Median  $IC_{50}$  values were used to select a representative value from multiple laboratories. A cut-off of  $<10 \mu\text{M}$  was used to remove interactions that were unlikely to occur due to the inability of the statins to reach such concentrations in the body.

#### *Suspected Adverse Drug Reaction (ADR) Data*

Suspected ADR data was obtained from the Medicines and Healthcare products Regulatory Agency's (MHRA) Yellow Card interactive Drug Analysis Profiles (iDAPs).[34]. Suspected ADR reports from January 2018 to August 2022 were collected for each statin. This data included the number of ADRs reported to the Yellow Card scheme with reports being categorised based on the MedDRA organ classification. Organ classes of interest were identified using percentages of the total number of ADRs for that drug; an organ class was used if it had  $\geq 10\%$  of the total ADRs for at least one of the five statins.

#### *Prescribing Data*

Prescribing data was obtained from OpenPrescribing Database[35] for the January 2018 to August 2022 period. Standardisation was performed by calculating the number of ADRs per 100,000  $R_x$  for each statin.

#### *Statistical Analysis*

A chi-squared analysis was done on the standardised ADRs per 100,000  $R_x$  using Microsoft Excel for Mac (version 16.67) to determine the statistical significance of suspected ADR signals ( $P$ -value  $< 0.05$ ).

#### *Ethical Approval*

No ethical approval was required as the study used publicly available open-source data that was fully anonymised.

## Results

Target vs drug	Atorvastatin (μM)	Fluvastatin (μM)	Pravastatin (μM)	Rosuvastatin (μM)	Simvastatin (μM)
----------------	-------------------	------------------	------------------	-------------------	------------------

### Physicochemical properties and pharmacokinetics

**Table 1** shows the properties of the statins. Rosuvastatin and pravastatin were predicted to be less likely than other statins to cause toxicity based on the LLE – both being > 5; atorvastatin had the smallest LLE suggesting it may have more off-target effects compared to other statins.

Fluvastatin was predicted to be the most likely to cross the BBB followed by simvastatin, pravastatin, rosuvastatin and atorvastatin based on the physicochemical properties that they possess: <450 Da MW, a tPSA < 90Å, molecule is basic or neutral, a  $\log_{10}D_{7.4}$  of 1-3, <2 HBA and <6 HBD and not being a substrate for P-glycoprotein transporter. Atorvastatin was found to be the most lipophilic which is reflected in its high volume of distribution ( $V_d$ ),

**Table 1.** Physicochemical and pharmacokinetic properties of the five statin tablet formulations. Key:  $c\log_{10}P$ , calculated partition coefficient; LLE, lipophilic ligand efficiency;  $\log_{10}D_{7.4}$  partition coefficient at pH 7.4; MW, Molecular Weight;  $pK_a$ , acid dissociation constant; tPSA, topological polar surface area; HB, hydrogen bond;  $C_{max}$ , peak serum concentration;  $V_d$ , volume of distribution; PPB, plasma protein binding. Highlighted properties are those that increase the chance of BBB penetration.

Property vs drug	Atorvastatin	Fluvastatin	Pravastatin	Rosuvastatin	Simvastatin
$c\log_{10}P$	5.39	3.83	1.65	1.92	4.46
$pIC_{50}$	8.06	7.85	7.52	8.35	7.59
LLE	2.67	4.02	5.87	6.43	3.13
$\log_{10}D_{7.4}$	2.43	1.05	-1.38	-1.24	4.46
MW (Da)	558.65	411.47	424.53	481.55	418.57
$pK_a$	4.31	4.54	4.21	4	Neutral
tPSA (Å)	111.79	82.69	124.29	140.92	72.83
HB Acceptors	5	4	6	7	5
HB Donors	4	3	4	3	1
Bioavailability (%)	12	24	17	20	<5
$C_{max}$ (nM)	118.5	687.78	189.57	39.04	130.71
Half-life (h)	14	2.3	1.5-2	19	1.9
$V_d$ (L)	381	330	0.5L/Kg	134	233
PPB	≥ 98%	> 98%	50%	90%	> 95%
P-Glycoprotein substrate	Yes	No	No	No	Likely
Liver CYP <sub>450</sub> metabolism	3A4	2C9, 3A4, 2C8	Minimal	Minimal	3A4, 3A5, 2C8, 2C9
Dosing regime	10-80mg OD	20-80mg OD/BID	10-40mg OD	5-20mg OD	10-80mg OD

### Target Affinity

**Table 2** shows the pharmacological interactions of the five statins as median  $IC_{50}$  values. Interactions with a respective  $IC_{50} \gg C_{max}$  were excluded from further analysis as it is unlikely that the statins would reach these clinically relevant concentrations in the body.

**Table 2.** Pharmacological interactions of the statins studied.

HMG-CoA Reductase	0.009	0.014	0.03	0.005	0.026
Solute carrier organic anion transporter family member 1B1 (OATP1B1)	0.81		3.6		7.9
Solute carrier organic anion transporter family member 1B3 (OATP1B3)	3.4		62		
Solute carrier organic anion transporter family member 2B1 (OATP2B1)			190		
Cytochrome P450 2C9		0.4			30
Cytochrome P450 3A4	5.1				30
Cytochrome P450 2C8					3.7
Cytochrome P450 2D6					30
Cytochrome P450 2C19					30
Cytochrome P450 1A2					30
Histone deacetylase 1	11.4				
Histone deacetylase 6	14.3				
Histone deacetylase 2	22.5				
Bile salt export pump	13	36.1	133	133	24.7
Multidrug resistance-associated protein 4	88.5	133	133	26.8	133
Canalicular multispecific organic anion transporter 1	133		133	133	79
Canalicular multispecific organic anion transporter 2	14.2	57	125	58.3	133
P-glycoprotein 1	289				26.1
Photoreceptor-specific nuclear receptor (NR2E3)		0.53			1.2
Squalene monooxygenase			10		
Solute carrier family 22 member 6 (hOAT1)			408		
Solute carrier family 22 member 7 (hOAT2)			352		
Solute carrier family 22 member 8 (hOAT3)			13.7		
Solute carrier family 22 member 11 (hOAT4)			591		
<b>C<sub>max</sub></b>	<b>0.12</b>	<b>0.69</b>	<b>0.19</b>	<b>0.04</b>	<b>0.13</b>

Fluvastatin (n=2) was found to have the most potential off-target interactions that were at clinically achievable concentrations (Cytochrome P450 2C9 and Photoreceptor-specific nuclear receptor (NR2E3), respectively). Rosuvastatin, pravastatin, atorvastatin, and simvastatin had no relevant off-target interactions (n=0).

Atorvastatin, pravastatin and simvastatin showed activity at OATP1B1 with atorvastatin having the most potent action with an  $IC_{50}$  of 0.81  $\mu$ M ( $C_{max}$  = 0.12  $\mu$ M); atorvastatin also showed activity at OATP1B3 (3.4  $\mu$ M).

Atorvastatin, fluvastatin and simvastatin showed activity at several CYP450 enzymes involved in their metabolism; CYP3A4 for atorvastatin with  $IC_{50}$  of 5.1  $\mu$ M, CYP2C9 for fluvastatin with an  $IC_{50}$  of 0.4  $\mu$ M and CYP2C8 for simvastatin with an  $IC_{50}$  of 3.7  $\mu$ M. Fluvastatin was twice as potent as simvastatin when acting on NR2E3 ( $IC_{50}$  = 0.53  $\mu$ M); and pravastatin was the only statin to cause inhibition on squalene monooxygenase with an  $IC_{50}$  of 10  $\mu$ M.

### *Adverse Drug Reactions*

The total number of each statin prescribed in the UK, the number of suspected ADRs, and their incidence rates for the selected organ classes from January 2018 - August 2022 alongside chi-squared statistical analysis results are presented in **Table 3**.

Atorvastatin was the most prescribed statin (226,846,930) followed by simvastatin (94,630,298), rosuvastatin (13,173,853), pravastatin (11,536,965) and then fluvastatin with the least prescriptions (496,892).

Fluvastatin had the most reported suspected ADRs per 100,000 prescriptions (5.64) followed by rosuvastatin (4.89), pravastatin (3.54), atorvastatin (2.11) and then simvastatin (1.41). Fatality incidence was similar across the statins with rates ranging between 0.00-0.03 per 100,000  $R_x$ .

**Table 3.** Summary of the selected Yellow Card ADR reporting data for the five statins in the UK. The numbers in the brackets are ADRs/100,000  $R_x$ .

	Atorvastatin	Fluvastatin	Pravastatin	Rosuvastatin	Simvastatin	P-values
Total Prescriptions	226846930	496892	11536965	13173853	94630298	-
Total ADRs	4782 (2.11)	28 (5.64)	408 (3.54)	644 (4.89)	1331 (1.41)	0.46
Total Fatalities	20 (0.01)	0 (0.00)	3 (0.03)	1 (0.01)	6 (0.01)	-
<b>Gastrointestinal disorders</b>						
Total ADRs	549 (0.242)	2 (0.403)	42 (0.364)	73 (0.554)	130 (0.137)	0.99
Total Fatalities	3 (0.001)	0 (0)	0 (0)	0 (0)	0 (0)	-
<b>General disorders and administration site conditions</b>						
Total ADRs	555 (0.245)	4 (0.805)	56 (0.485)	65 (0.493)	150 (0.159)	0.96
Total Fatalities	5 (0.002)	0 (0)	2 (0.017)	0 (0)	2 (0.002)	-
<b>Injury, poisoning and procedural complications</b>						
Total ADRs	161 (0.071)	0 (0)	25 (0.217)	8 (0.061)	93 (0.098)	0.99
Total Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.001)	-
<b>Investigations</b>						
Total ADRs	279 (0.123)	1 (0.201)	8 (0.069)	18 (0.137)	75 (0.079)	-
Total Fatalities	0 (0)	0 (0)	1 (0.009)	0 (0)	0 (0)	-
<b>Musculoskeletal and connective tissue disorders</b>						
Total ADRs	1057 (0.466)	12 (2.415)	77 (0.667)	193 (1.465)	306 (0.323)	0.58
Total Fatalities	3 (0.001)	0 (0)	0 (0)	0 (0)	1 (0.001)	-
<b>Nervous system disorders</b>						
Total ADRs	533 (0.235)	4 (0.805)	45 (0.390)	93 (0.706)	113 (0.119)	0.94
Total Fatalities	1 (0.0004)	0 (0)	0 (0)	0 (0)	0 (0)	-
<b>Psychiatric disorders</b>						
Total ADRs	259 (0.114)	1 (0.201)	33 (0.286)	40 (0.304)	76 (0.080)	1
Total Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.001)	-
<b>Skin and subcutaneous tissue disorders</b>						
Total ADRs	367 (0.162)	1 (0.201)	41 (0.355)	59 (0.448)	100 (0.106)	0.99
Total Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	-

There was no significant difference between the suspected ADRs per 100,000  $R_x$  for the statins ( $\chi^2$ -analysis), in any of the organ classes however, the musculoskeletal and connective tissue class did have a noticeably different  $P$ -value (0.58) compared to all other organ classes.

Within the musculoskeletal and connective tissue organ class, fluvastatin had the highest incidence of ADRs (2.415) followed by rosuvastatin (1.465), pravastatin (0.667), atorvastatin (0.466) and lastly simvastatin (0.323). Atorvastatin and simvastatin had a 0.001 incidence rate per 100,000  $R_x$  for fatalities whereas the other three statins had no reports in this time frame. Further chi-squared statistical analysis was performed within the musculoskeletal and connective tissue organ class (**Table 4**).



**Table 4.** Chi-squared analysis results from comparing the statins suspected ADR reports per 100,000  $R_x$  within the musculoskeletal and connective tissue organ class.

Statins	<i>P</i> -value
fluvastatin vs atorvastatin	0.15
fluvastatin vs pravastatin	0.17
fluvastatin vs rosuvastatin	0.17
fluvastatin vs simvastatin	0.14
atorvastatin vs simvastatin	0.35
atorvastatin vs pravastatin	0.48
atorvastatin vs rosuvastatin	0.49
pravastatin vs rosuvastatin	0.59
pravastatin vs simvastatin	0.41
rosuvastatin vs simvastatin	0.41

There was no statistically significant difference between any pair of statins for  $p < 0.05$  however the  $p$ -values for fluvastatin were noticeably pronounced than for other statins.

## Discussion

Many of the polypharmacological interactions are unlikely to occur as the concentrations required for an effect are not clinically relevant based on the  $C_{max}$  of the statins (**Table 1**). Without the accumulation of statin, it is unlikely that plasma concentrations of statin will reach these figures. It is possible for fluvastatin to accumulate in patients with hepatic impairment[36] due to it being primarily excreted via the bile with extensive pre-systemic metabolism; this may contribute to fluvastatin having the highest incidence of ADRs per 100,000  $R_x$  (**Table 3**). Fluvastatin had the highest ADR incidence in multiple organ classes however it was prescribed over twenty-fold less than the next least prescribed statin, pravastatin.

### ADR Incidence

Overall, no significant difference was found between the statins and any organ class for  $P < .05$  (**Table 3**). This suggests that the statins could have a similar class effect not individual differing off-target pharmacological mechanisms.

For the musculoskeletal and connective tissue organ class ( $P = .58$ ) there was no statistically significant difference between the statins however, when compared to the  $P$  values for other organ classes - a difference in risk emerges. Further analysis within the musculoskeletal and connective tissue organ class showed no statistically significant difference (**Table 4**) however, fluvastatin compared to other statin-pairs had lower  $P$  values and also had the highest suspected ADR incidence across multiple organ classes – which was unexpected.

Fluvastatin is a low-medium intensity statin.[37] The National Institute for Health and Care Excellence (NICE) guidelines, recommend a high intensity statin as first line treatment for patients at risk of cardiovascular disease.[38] Another contributing factor is that fluvastatin is the only statin indicated for use after percutaneous coronary intervention, a procedure which is also known to cause some pain post-operatively.[39] The low prescribing rate, potential for accumulation and patient-comorbidities could explain the unexpectedly high suspected ADR incidence of fluvastatin.

Chi-squared analysis has shown that there was no significant difference between the statins in the musculoskeletal and connective tissue organ class and amongst the remaining ADR organ classes. These findings confirm a recent meta-analysis[14] that there was no clear evidence that the risk ratios for musculoskeletal symptoms differed between statins; it did however find that higher intensity statins caused an increased risk of muscle pain or weakness compared to moderate intensity statins. There is no sequential change of intensity

between the statins when looking at the suspected muscle ADR incidence (**Table 3**); Rosuvastatin is classed as moderate-high statin which had the next highest suspected muscle ADR incidence followed by pravastatin which is classed as low-moderate statin.

These findings do also align with another large-scale meta-analysis[40] which found that patients were less likely to experience myalgia with simvastatin than with atorvastatin in a pairwise meta-analysis; it also found no significant difference between the statins when collectively comparing 1,986 myalgia events in a drug-level network meta-analysis.

#### *Physicochemical properties*

There does not appear to be a clear relationship between the physicochemical properties (**Table 1**) and the suspected ADR incidence. Rosuvastatin and pravastatin are the most hydrophilic compared to the remaining statins based on their negative  $\log_{10}D^{7.4}$  values. This prevents them from passively diffusing through tissue and requires the use of carriers to facilitate their uptake into the liver.[41] This should in theory increase selectivity and so reduce uptake into other tissues such as muscle tissue however, this is not reflected in the suspected muscle ADR incidence as the lipophilic atorvastatin and simvastatin had smaller suspected incidence values compared to the two hydrophilic statins (rosuvastatin and pravastatin).

Based on the physicochemical properties, fluvastatin was predicted as most likely to cross the BBB followed by simvastatin, pravastatin, rosuvastatin and atorvastatin. Previous studies have found that the lipophilic statins such as atorvastatin, fluvastatin and simvastatin can easily cross the BBB whilst hydrophilic statins are less likely to achieve this at clinically used concentrations. [42] There does not appear to be a relationship between the statins which were predicted as more likely to cross the BBB and ADR incidence in the nervous system and psychiatric disorder categories. It is unclear based on current research whether there are any causative links between statins and these types of disorders or whether some individuals are predisposed to these conditions and are affected by them coincidentally during their treatment with statins.[43]

#### *Pharmacological interactions*

Atorvastatin, pravastatin, and simvastatin showed modest activity at OATP1B1 transporter whilst atorvastatin also showed activity at OATP1B3. Statins are known to be substrates of these organic anion transporter polypeptides which facilitate uptake into the liver.[44] Mutations in the SLCO1B1 gene which encodes for OATP1B1 have been linked to decreased hepatic uptake of statins and increased systemic exposure,[45] increasing the risk of myopathy. Patients taking inhibitors of these transporters such as ciclosporin[46] are advised to reduce their statin dose to prevent ADRs because of increased statin exposure.

Fluvastatin showed activity at CYP2C9, atorvastatin at CYP3A4 and simvastatin at CYP2C8. These are enzymes that are involved in the metabolism of these statins and unlikely to have a role in ADRs unless the statins are taken concomitantly with inhibitors of these enzymes, in turn increasing systemic exposure to the statin. Inhibitors of cytochrome P450 enzymes are less likely to affect rosuvastatin and pravastatin as these are metabolised via other pathways.[41]

Pravastatin showed inhibition of squalene monooxygenase which is another rate-limiting enzyme in the cholesterol synthesis pathway acting downstream of HMG-CoA reductase.[47] Little evidence is available for the clinical relevance of squalene monooxygenase inhibition, with animal studies showing symptoms of dermatitis and neuropathy due to squalene monooxygenase inhibitors.[48]

Fluvastatin and simvastatin showed activity at the photoreceptor-specific nuclear receptor (NR2E3) which is involved in photoreceptor proliferation. Mutations of its gene have been shown to cause retinal degeneration in animal studies and other eye disorders.[49] It is unclear whether this interaction has any significance for statins and in causing ADRs, no studies of clinical relevance regarding this interaction were identified.

#### **Limitations**

Prescribing data was available from November 2017 until August 2022 however due to the format in which the ADR data was available from the MHRA Yellow card scheme, data was extracted from January 2018 (excluding the data available from 2017). However, this ensured that the suspected ADR incidence per 100,000  $R_x$  for 2017 was not inflated due to ADRs being included for the two months in 2017 where prescribing data was not available.

Reports from the Yellow Card Scheme are suspected reports and therefore no causal relationship must be demonstrated or evidenced before submitting a report. Therefore, reported ADRs in any registry may have no defined relationship to the pharmacology of the statins. Comparison of the ADR incidence for a statin against an average incidence was used to ensure relevant ADRs were highlighted. Underreporting of ADRs is also a common issue with the pharmacovigilance schemes leading to ADRs going undetected.[50] Information such as other drug use and health conditions are not available from the Yellow Card scheme and so it is not possible to establish causality through this data alone.

The musculoskeletal and connective tissue disorders organ class was analysed as a whole and so included connective tissue disorders in the statistical analysis. Interactions with human proteins were extracted from the ChEMBL database which necessarily does not contain every possible interaction which the statins could have in the human body. Furthermore, multiple  $IC_{50}$  values were available for each protein and so a median value was used.

## Conclusions

Statins have proven to be effective in the reduction of cardiovascular events with a small risk of muscle related ADRs that is outweighed by the benefits to the patient. The study found that there was no significant difference between the statins across the organ classes investigated and specifically in the musculoskeletal and connective tissue disorder category. Fluvastatin was found to have an unexpectedly high suspected ADR incidence across multiple organ classes which initially could be attributed to lower prescribing rates than the other statins but was corrected for in this study based on prescribing levels.

Pharmacological interactions of the statins included the cytochrome P450 enzymes and the organic anion transporters. New interactions with NR2E3 and squalene monooxygenase were identified. However, a relationship to statin ADRs was not clear.

## Conflict of Interest

There is no conflict of interest to be disclosed.

## Availability of Data

The data that support the findings of this study are openly available in the Supporting Information file.

## References

1. Rang HP. Drugs affecting major organ systems. In: Rang and Dale's Pharmacology. 9th ed. Edinburgh: Churchill Livingstone; 2020:314-315.
2. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science*. 1986;232(4746):34-47. doi:10.1126/science.3513311
3. Mortensen MB, Nordestgaard BG. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 Years: A contemporary primary prevention cohort. *The Lancet*. 2020;396(10263):1644-1652. doi:10.1016/s0140-6736(20)32233-9
4. Abdullah SM, Defina LF, Leonard D, et al. Long-term association of low-density lipoprotein cholesterol with cardiovascular mortality in individuals at low 10-year risk of atherosclerotic cardiovascular disease. *Circulation*. 2018;138(21):2315-2325. doi:10.1161/circulationaha.118.034273
5. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian simvastatin survival study (4S). *The Lancet*. 1994;344(8934). doi:10.1016/s0140-6736(94)90566-5

6. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: Meta-analysis of individual data from 27 randomised trials. *The Lancet*. 2012;380(9841):581-590. doi:10.1016/s0140-6736(12)60367-5
7. NHS. Statins. <https://www.nhs.uk/conditions/statins/>. Published 2022. Accessed December 15, 2022.
8. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. *The Lancet*. 2000;356(9237):1255-1259. doi:10.1016/s0140-6736(00)02799-9
9. Pedro-Botet J, Núñez-Cortés JM, Flores JA, Rius J. Muscle symptoms related with statin therapy in general practice. *Atherosclerosis*. 2015;241(1). doi:10.1016/j.atherosclerosis.2015.04.957
10. Lotteau S, Ivarsson N, Yang Z, et al. A mechanism for statin-induced susceptibility to myopathy. *JACC: Basic to Translational Science*. 2019;4(4):509-523. doi:10.1016/j.jacbts.2019.03.012
11. Isackson PJ, Wang J, Zia M, et al. RYR1 and CACNA1S genetic variants identified with statin-associated muscle symptoms. *Pharmacogenomics*. 2018;19(16):1235-1249. doi:10.2217/pgs-2018-0106
12. Chou R, Cantor A, Dana T. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: A Systematic Review for the U.S. Preventive Services Task Force. National Center for Biotechnology Information. <https://www.ncbi.nlm.nih.gov/books>. Published August 2022. Accessed January 7, 2023.
13. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Annals of Pharmacotherapy*. 2002;36(2):288-295. doi:10.1345/aph.1a289
14. Reith C, Baigent C, Blackwell L, et al. Effect of statin therapy on muscle symptoms: An individual participant data meta-analysis of large-scale, randomised, double-blind trials. *The Lancet*. 2022;400(10355):832-845. doi:10.1016/s0140-6736(22)01545-8
15. Jones, L., Jones, A. M. Suspected Adverse Drug Reactions of the Type 2 Antidiabetic Drug class Dipeptidyl-Peptidase IV inhibitors (DPP4i): Can polypharmacology help explain? *Pharmacol. Res. Perspect.* 2022, 10(6) e01029.
16. Salim, H, Jones, A.M. Angiotensin II Receptor Blockers (ARBs) and Manufacturing Contamination: A Retrospective National Register Study into suspected associated adverse drug reactions. *Brit. J. Clin. Pharmacol.* 2022, 88(11), 4812-4827.
17. Sandhu, D., Antolin, A.A., Cox, A. R., Jones, A.M. Identification of different side effects between PARP inhibitors and their polypharmacological multi-target rationale. *Brit. J. Clin. Pharmacol.* 2022, 88, 742-752.
18. Matharu, K., Chana, K., Ferro, C., Jones, A. M. Polypharmacology of clinical sodium glucose co-transport protein 2 inhibitors and relationship to suspected adverse drug reactions. *Pharmacol. Res. Perspect.* 2021, 9, e00867.
19. Ferro, C. J., Solkhon, F., Jalal, Z., Al-Hamid, A. M., Jones, A. M.\* "Relevance of physicochemical properties and functional pharmacology data to predict the clinical safety profile of direct oral anticoagulants" *Pharmacol. Res. Perspect.* 2020, 8, e00603.
20. European Molecular Biology Laboratory. ChEMBL Database. EMBL-EBI homepage. <https://www.ebi.ac.uk/chembl/>. Published 2018. Accessed November 30, 2022.
21. Electronic Medicines Compendium. Home - electronic medicines compendium (emc). <https://www.medicines.org.uk/emc>. Published 2022. Accessed November 30, 2022.
22. Van de Waterbeemd H, Camenisch G, Folkers G, Chretien JR, Raevsky OA. Estimation of blood-brain barrier crossing of drugs using molecular size and shape, and H-bonding descriptors. *Journal of Drug Targeting*. 1998;6(2):151-165. doi:10.3109/10611869808997889
23. Pajouhesh H, Lenz GR. Medicinal chemical properties of successful Central Nervous System Drugs. *Neurotherapeutics*. 2005;2(4):541-553. doi:10.1602/neurorx.2.4.541
24. Hopkins AL, Keserü GM, Leeson PD, Rees DC, Reynolds CH. The role of ligand efficiency metrics in drug discovery. *Nature Reviews Drug Discovery*. 2014;13(2):105-121. doi:10.1038/nrd4163
25. Hann MM. Molecular obesity, potency and other addictions in Drug Discovery. *MedChemComm*. 2011;2(5):349-355. doi:10.1039/c1md00017a
26. Lins RL, Matthys KE, Verpooten GA, et al. Pharmacokinetics of atorvastatin and its metabolites after single and multiple dosing in hypercholesterolaemic haemodialysis patients. *Nephrology Dialysis Transplantation*. 2003;18(5):967-976. doi:10.1093/ndt/gfg048
27. Xu HR, Chen WL, Chu NN, Li XN, Zhu JR. The difference in pharmacokinetics and pharmacodynamics between extended-release fluvastatin and immediate-release fluvastatin in healthy Chinese subjects. *Journal of Biomedicine and Biotechnology*. 2012;2012:1-4. doi:10.1155/2012/386230
28. Deng M, Xue H, Liu H, Cao L. Study on bioequivalence of pravastatin sodium tablets in healthy volunteers. *Journal of Chinese Pharmaceutical Sciences*. 2005;40(6):451-453.

- [https://www.researchgate.net/publication/288627404\\_Study\\_on\\_bioequivalence\\_of\\_pravastatin\\_sodium\\_tablets\\_in\\_healthy\\_volunteers](https://www.researchgate.net/publication/288627404_Study_on_bioequivalence_of_pravastatin_sodium_tablets_in_healthy_volunteers). Accessed December 13, 2022.
29. Martin PD, Warwick MJ, Dane AL, et al. Metabolism, excretion, and pharmacokinetics of rosuvastatin in healthy adult male volunteers. *Clinical Therapeutics*. 2003;25(11):2822-2835. doi:10.1016/s0149-2918(03)80336-3
30. FDA: CENTER FOR DRUG EVALUATION AND RESEARCH. Drug approval package. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S). [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/206679Orig1s000ClinPharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206679Orig1s000ClinPharmR.pdf). Published 2016. Accessed December 16, 2022.
31. DrugBank online: Database for Drug and Drug Target Info. DrugBank Online | Database for Drug and Drug Target Info. <https://go.drugbank.com/>. Published 2022. Accessed December 18, 2022.
32. Alakhali K. Pharmacokinetic of simvastatin study in Malaysian subjects. *IOSR Journal of Pharmacy (IOSRPHR)*. 2013;3(1):46-51. doi:10.9790/3013-3110465133. Goard CA, Mather RG, Vinopal B, et al. Differential interactions between statins and P-glycoprotein: Implications for exploiting statins as Anticancer Agents. *International Journal of Cancer*. 2010;127(12):2936-2948. doi:10.1002/ijc.25295
34. Medicines and Healthcare products Regulatory Agency. What is being reported. YellowCard. <https://yellowcard.mhra.gov.uk/idaps>. Published 2022. Accessed November 30, 2022.
35. Bennett Institute for Applied Data Science, Department of Primary Care Health Sciences, University of Oxford. All chemicals. OpenPrescribing. <https://openprescribing.net/chemical/>. Published 2022. Accessed December 5, 2022.
36. Datapharm Ltd. Fluvastatin 20 mg capsules. Fluvastatin 20 mg Capsules - Summary of Product Characteristics (SmPC) - (emc). [https://www.medicines.org.uk/emc/product/4465/smpc#CLINICAL\\_PRECAUTIONS](https://www.medicines.org.uk/emc/product/4465/smpc#CLINICAL_PRECAUTIONS). Published 2022. Accessed December 20, 2022.
37. National Institute for health and Care Excellence. Appendix A: Grouping of statins: Cardiovascular disease: Risk assessment and reduction, including lipid modification: Guidance. <https://www.nice.org.uk/guidance/cg181/chapter/appendix-a-grouping-of-statins>. Published July 18, 2014. Accessed January 1, 2023.
38. National Institute for health and Care Excellence. Recommendations: Cardiovascular disease: Risk assessment and reduction, including lipid modification: Guidance. <https://www.nice.org.uk/guidance/cg181/chapter/Recommendations#lipid-modification-therapy-for-the-primary-and-secondary-prevention-of-cvd-2>. Published July 18, 2014. Accessed January 1, 2023.
39. Mansour M, Carrozza JP, Kuntz RE, et al. Frequency and outcome of chest pain after two new coronary interventions (atherectomy and stenting). *The American Journal of Cardiology*. 1992;69(17):1379-1382. doi:10.1016/0002-9149(92)90885-3
40. Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins. *Circulation: Cardiovascular Quality and Outcomes*. 2013;6(4):390-399. doi:10.1161/circoutcomes.111.000071
41. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: An update. *Fundamental and Clinical Pharmacology*. 2005;19(1):117-125. doi:10.1111/j.1472-8206.2004.00299.x
42. Wood WG, Eckert GP, Igbavboa U, Müller WE. Statins and neuroprotection. *Annals of the New York Academy of Sciences*. 2010;1199(1):69-76. doi:10.1111/j.1749-6632.2009.05359.x
43. McFarland A, Anoopkumar-Dukie S, Arora D, et al. Molecular mechanisms underlying the effects of statins in the Central Nervous System. *International Journal of Molecular Sciences*. 2014;15(11):20607-20637. doi:10.3390/ijms151120607
44. Shitara Y. Clinical importance of OATP1B1 and OATP1B3 in drugdrug interactions. *Drug Metabolism and Pharmacokinetics*. 2011;26(3):220-227. doi:10.2133/dmpk.dmpk-10-rv-094
45. Niemi M. Transporter pharmacogenetics and statin toxicity. *Clinical Pharmacology & Therapeutics*. 2009;87(1):130-133. doi:10.1038/clpt.2009.197
46. Shitara Y, Takeuchi K, Nagamatsu Y, Wada S, Sugiyama Y, Horie T. Long-lasting inhibitory effects of cyclosporin A, but not tacrolimus, on OATP1B1- and OATP1B3-mediated uptake. *Drug Metabolism and Pharmacokinetics*. 2012;27(4):368-378. doi:10.2133/dmpk.dmpk-11-rg-096
47. Matzno S, Yamauchi T, Gohda M, et al. Inhibition of cholesterol biosynthesis by squalene epoxidase inhibitor avoids apoptotic cell death in L6 myoblasts. *Journal of Lipid Research*. 1997;38(8):1639-1648. doi:10.1016/s0022-2275(20)37182-0
48. Chugh A. Squalene epoxidase as hypocholesterolemic drug target revisited. *Progress in Lipid Research*. 2003;42(1):37-50. doi:10.1016/s0163-7827(02)00029-2
49. Cheng H. Photoreceptor-specific nuclear receptor NR2E3 functions as a transcriptional activator in rod photoreceptors. *Human Molecular Genetics*. 2004;13(15):1563-1575. doi:10.1093/hmg/ddh173

50. Hazell L, Shakir SA. Under-reporting of Adverse Drug Reactions. *Drug Safety*. 2006;29(5):385-396. doi:10.2165/00002018-200629050-00003