MiniReview

Interaction Potential between Clarithromycin and Individual Statins – a Systematic Review

Mette Marie Hougaard Christensen 1,2
Maija Bruun Haastrup 1,3
Thomas Øhlenschlæger 1
Peter Esbech 1
Sidsel Arnspang Pedersen 1
Ann-Cathrine Bach Dunvald 1
Tore Bjerregaard Stage 3
Daniel Pilsgaard Henriksen 1,3
Andreas James Thstrup Pedersen 1

1. Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark
2. Department of Clinical Research, University of Southern Denmark, Odense, Denmark
3. Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark

Running title: Interaction between Clarithromycin and Statins

Key words: Mini-review, Drug-drug interaction, clarithromycin, statins, case report

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bcpt.13343. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.
Conflict of interest: The authors declare no conflict of interest.

(Received 19 September 2019; Accepted 11 October 2019)

Correspondence

Mette Marie Hougaard Christensen
Associate Professor, Chief Physician, PhD
Department of Clinical Biochemistry and Pharmacology
Odense University Hospital
JB Winsløwsvej 19, 2
5000 Odense C, Denmark
E-mail: mmchristensen@health.sdu.dk
Phone: +45 6550 9185
Abstract

The high prevalence of statin and clarithromycin utilization creates potential for overlapping use. The objectives of this MiniReview were to investigate the evidence base for drug-drug interactions between clarithromycin and currently marketed statins and to present management strategies for these drug combinations. We conducted a systematic literature review following PRISMA guidelines with English language studies retrieved from PubMed and EMBASE (from inception through March 2019). We included 29 articles (16 case reports, 5 observational, 5 clinical pharmacokinetic and 3 in vitro studies). Based on mechanistic/clinical studies involving clarithromycin or the related macrolide erythromycin (both strong inhibitors of CYP3A4 and of hepatic statin uptake transporters OATP1B1 and OATP1B3), clarithromycin is expected to substantially increase systemic exposure to simvastatin and lovastatin (>5-fold increase in area under the plasma concentration time curve (AUC)), moderately increase AUCs of atorvastatin and pitavastatin (2-4-fold AUC increase) and slightly increase pravastatin exposure (≈ 2-fold AUC increase) while having little effect on fluvastatin or rosuvastatin. The 16 cases of statin-clarithromycin adverse drug reactions (rhabdomyolysis (n = 14) or less severe clinical myopathy) involved a CYP3A4-metabolized statin (simvastatin, lovastatin or atorvastatin). In line, a cohort study found concurrent use of clarithromycin and CYP3A4-metabolized statins to be associated with a doubled risk of hospitalisation with rhabdomyolysis or other statin-related adverse events as compared with azithromycin-statin co-administration. If clarithromycin is necessary, we recommend 1) avoiding co-administration with simvastatin, lovastatin or atorvastatin; 2) withholding or dose-reducing pitavastatin; 3) continuing pravastatin therapy with caution, limiting pravastatin dose to 40 mg daily and 4) continuing fluvastatin or rosuvastatin with caution.
Introduction and background

HMG-CoA reductase inhibitors, also known as statins, are widely used as the mainstay therapy for the management of dyslipidaemia, including primary and secondary prevention of cardio- and cerebrovascular disease (1). Although considered efficacious and safe, statins are associated with adverse effects, among which skeletal muscle toxicity is the most common one (2). The frequency of statin-related skeletal muscle toxicity varies according to definition and dose. Mild myalgias have been reported in up to 10% of statin-treated patients, while extensive skeletal muscle damage including its most severe form rhabdomyolysis is much less common (2). Increased statin exposure is an important risk factor for statin-related skeletal muscle toxicity (3). Hence, the risk of this adverse drug reaction increases with concurrent use of drugs affecting statin disposition with subsequent accumulation of the statin or its metabolites (4). It is estimated that over 200 million patients are on statin therapy worldwide (5).

The pharmacokinetic handling of statins, and subsequent potential for drug-drug interactions (DDIs) differs considerably on a medication-by-medication basis. Hence, individual statins differ markedly both in degree of cytochrome P450 (CYP)-mediated metabolism and, for statins which undergo significant phase I oxidative metabolism, in the individual CYP isoenzymes involved. Furthermore, the degree to which select membrane transporters impact drug disposition may vary markedly between specific statins (6).

Macrolides are commonly used antibiotics (7). Clarithromycin, a macrolide antibiotic, with indications of use including treatment of atypical pneumonia and infections caused by Helicobacter pylori (8), acts as a strong CYP3A4 inhibitor (9) and has been shown to inhibit the hepatic statin uptake transporters organic anion transporting polypeptide (OATP)1B1 and OATP1B3 in transfected human kidney cell cultures (10). In line with such inhibitory potential, clarithromycin has been associated with an increased risk of several statin-related adverse events, including skeletal muscle toxicity (11,12).

Recently, the Drug Information Center at Odense University hospital was contacted regarding a fatal case of rhabdomyolysis subsequent to initiation of clarithromycin in a patient already treated with simvastatin. This case prompted us to perform a systematic literature review of mechanistic and clinical evidence concerning the interaction potential between clarithromycin and each of the seven statins currently available for clinical use internationally, starting with a
brief overview of statin pharmacokinetics and genetic factors with established effect on systemic statin exposure. Finally, based on the literature review, we present suggestions for strategies on how to manage such interactions in a clinical setting.

**Overview of statin pharmacokinetics and pharmacogenetics impacting systemic statin exposure**

Simvastatin and lovastatin are prodrugs that are absorbed in an inactive lactone form with subsequent conversion in the liver to their active moieties; atorvastatin, fluvastatin, pitavastatin, pravastatin and rosuvastatin are administered as active compounds (in acid form). Atorvastatin and, particularly, lovastatin and simvastatin are predominately metabolized by CYP3A4. Fluvastatin’s biotransformation involves multiple isoenzymes, primarily CYP2C9, while pitavastatin, pravastatin and rosuvastatin undergo limited hepatic metabolism (13). Regarding statin DDIs, of particular importance is the potential for substantially increased systemic exposure to CYP3A4-metabolized statins following co-treatment with drugs that are strong inhibitors of CYP3A4. For example, co-administration of simvastatin with the HIV-protease inhibitors saquinavir (weak CYP3A4 inhibitor) plus ritonavir (very potent CYP3A4 inhibitor) has been described to increase simvastatin exposure by as much as 32-fold (14).

Besides differences in oxidative metabolism, statins also vary in their affinity for membrane transporters involved in processes such as intestinal absorption, hepatic uptake, biliary excretion and/or renal elimination (15). The OATPs are considered the key mediators of hepatic statin uptake, with OATP1B1 (gene name *SLCO1B1*) considered the most important influx transporter related to statins (16). OATP1B1 is located on the basolateral membrane of hepatocytes and facilitates the uptake from portal blood of all currently marketed statins (2). The activity of OATP1B1 is impacted by genetic polymorphism; approximately 15-20% of Caucasians, 10-15% of Asians and 2% of African Americans carry at least one low-activity *SLCO1B1* allele (17).

Considerable drug-specific variability exists as concerns the influence of OATP1B1 on the pharmacokinetics of individual statins. In individuals with low OATP1B1 function (i.e. homozygous for the *SLCO1B1* decreased-function allele (rs4149056, T521C, encoding OATP1B1:V174A)), the area under the plasma concentration-time curve (AUC) of simvastatin acid (i.e. the main active form of the prodrug simvastatin) has been reported to be 3.2-fold higher.
than in controls with normal OATP1B1 function (18). Notably, individuals with intermediate (heterozygous for the SLCO1B1 decreased-function allele) or low OATP1B1 function are at an increased risk of clinical simvastatin-associated myopathy (odds ratio 4.5 and 16.9, respectively, at simvastatin 80 mg daily) (19). While association between SLCO1B1 genotype and risk of myopathy has been clearly established only for simvastatin (6), low OATP1B1 function has been shown to affect the pharmacokinetics of other statins to varying extents: for lovastatin acid, pitavastatin, atorvastatin, pravastatin and rosuvastatin, AUC has been found to be 3.9-fold, 3.1-fold, 2.4-fold, 1.9-fold and 1.6-fold higher, respectively, as compared to individuals with wild-type SLCO1B1 alleles (20–23). Fluvastatin disposition is not significantly affected by SLCO1B1 polymorphism (21). Less studied influx transporters relevant for hepatic uptake of specific statins include OATP1B3 (rosuvastatin, fluvastatin and, to a minor extent, pitavastatin and pravastatin) as well as the sodium-dependent taurocholate co-transporting peptide NTCP (rosuvastatin) (24). Aside from OATP1B1, the breast cancer resistance protein (BCRP, encoded by ABG2) comprises a second transporter with established effect on the disposition of several statins. BCRP is an efflux transporter expressed in e.g. intestinal enterocytes, in kidney proximal tubules cells and on the canalicular membrane of hepatocytes (25) and, hence, may regulate statin absorption as well as renal and biliary excretion. Among several ABCG2 polymorphisms, the reduced-function 421C>A (rs2231142) allele represents the variant with most well-established effect on statin pharmacokinetics (25). The prevalence of the 421C>A polymorphism is highest in Asian populations (25-35%), followed by Caucasian (10-15%) and African American (0-5%) populations (26). In individuals with the ABCG2 c.421 AA genotype, the AUCs of rosuvastatin and simvastatin acid have been shown to be 2.4-fold and 1.2-fold greater, respectively, while those of both atorvastatin and fluvastatin were 1.7-fold higher, as compared to ABCG2 c.421 TT-genotyped individuals; lovastatin, pitavastatin and pravastatin pharmacokinetics are not significantly affected by ABCG2 genotype (24,27–29). In vitro studies have found atorvastatin, lovastatin and simvastatin - but not fluvastatin, pravastatin or rosuvastatin - to be substrates of P-glycoprotein (P-gp), an efflux transporter located in a range of tissues, including the gastrointestinal tract as well as the liver and kidneys (30). The role of P-gp in DDIs involving statins is unclear. Based on studies involving digoxin, a specific P-gp probe substrate, the risk of statin-related adverse events due to P-gp inhibition alone by clarithromycin appears limited: in 18 healthy volunteers,
clarithromycin 500 mg twice daily for seven days increased digoxin \( \text{AUC}_{0-24} \) < 1.5-fold (31). However, it should be noted that the mean half-life of digoxin was prolonged from 32.5 hours (pre-clarithromycin) to 56.3 hours (post-clarithromycin) (31). Hence, the use of AUC values truncated at 0-24 hours may have underestimated the true extent of the interaction.

The CYP enzymes and transporters of most importance for individual statins’ metabolism or disposition – and the pathway(s) through which clarithromycin may accordingly affect statin pharmacokinetics – are shown in Figure 1 (24).

MiniReview:

Materials and methods

We conducted a literature search following the PRISMA guidelines for systematic reviews. A search string was created for PubMed (Medline): (("hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "statins"[All Fields] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[All Fields] OR "Atorvastatin"[Mesh] OR "Atorvastatin"[All Fields]) OR "fluvastatin"[Mesh] OR "fluvastatin"[All Fields] OR "lovastatin"[Mesh] OR "lovastatin"[All Fields] OR "pitavastatin"[Mesh] OR "pitavastatin"[All Fields] OR "Pravastatin"[Mesh] OR "Pravastatin"[All Fields] OR "Rosuvastatin Calcium"[Mesh] OR "Rosuvastatin"[All Fields] OR "Simvastatin"[Mesh] OR "Simvastatin"[All Fields]) AND ("drug interaction" [All fields] OR "drug interactions" [All fields]) AND ("Clarithromycin"[Mesh] OR "Clarithromycin"[All fields]) AND (English[lang]). Likewise, a search string was created for EMBASE (Exerpta Medica, Elsevier; Ovid): ((Hydroxymethylglutaryl-coa reductase inhibitors) OR (Hydroxymethylglutaryl-coa AND reductase AND inhibitors) OR statins OR (hydroxymethylglutaryl-CoA Reductase Inhibitors) OR (Hydroxymethylglutaryl-CoA Reductase Inhibitors) OR Atorvastatin OR fluvastatin OR lovastatin OR pitavastatin OR Pravastatin OR Rosuvastatin OR Simvastatin) AND ((drug interaction) OR (drug interactions) OR (interaction) OR (interactions)) AND (Clarithromycin) limit to (English language and (article or letter)). Both databases were searched from inception to the end of March 2019. Additional records identified
through Stockley’s drug-interaction information database were added. Only articles reporting on original data on the interaction between clarithromycin and statins were eligible for inclusion.

**Results**

The search revealed 261 articles on EMBASE, 60 articles on PubMed and four through Stockley’s drug-interaction information database. After removing duplicates, a total of 283 articles were left. The initial screening of the articles by titles and abstracts excluded 238 articles, because they were off topic. Full-text screening excluded another 16 articles, as these did not have specific information on the potential interaction between clarithromycin and statins or did not contain original data. Finally, included articles were cross-referenced for additional original publications. No additional articles were found. The included articles consist of 16 case reports, 5 observational, 5 clinical pharmacokinetic and 3 *in vitro* studies. The entire selection process is illustrated by flow diagram (Figure 2.).

**The in vitro evidence of drug-drug interactions between clarithromycin and statins**

Our literature search revealed three *in vitro* studies, summarized in Table 1, examining clarithromycin’s inhibitory potential on OATP1B3- and/or OATP1B1-mediated uptake of a statin (atorvastatin, pitavastatin or pravastatin) (32–34). Each study identified clarithromycin as an OATP inhibitor, with reported results consistent with clarithromycin having the potential to perpetrate clinically relevant drug-statin interactions as indicated by $[I]_1/IC_{50}$-values ≥ 0.1 (35) ($IC_{50}$: half-maximal inhibitory concentration; $[I]_1$: mean steady-state total maximum plasma concentration ($C_{max}$) following administration of highest recommended clinical inhibitor dose). In (32), clarithromycin at concentrations of 10 µM and 100 µM led to reductions of 36% and 76%, respectively, in intracellular accumulation of pravastatin in human embryonic kidney (HEK)-OATP1B1 cells, while addition of 100 µM clarithromycin reduced OATP1B3-mediated pravastatin uptake by 63%. Seithel et al. (33) also studied the effects of other macrolides on OATP1B1- and OATP1B3-mediated statin uptake: roxithromycin inhibited OATP1B1-facilitated pravastatin transport at both the low (10 µM) and the high (100 µM) concentration, erythromycin and roxithromycin each inhibited both OATP1B1- and OATP1B3-mediated pravastatin uptake at concentrations of 100 µM, while azithromycin (both concentrations) did not affect the activity of either transporter (32). The two other studies (33,34) made *in vitro-in vivo* extrapolations,
calculating predicted 2-fold (pitavastatin) (33) and 3.7-6.2-fold (atorvastatin) (34) increases in statin AUC following clarithromycin’s perturbation of individual OATPs (see Table 1). Our systematic literature search did not uncover an in vitro study examining clarithromycin’s inhibition of CYP3A4 or BCRP using a statin as probe substrate. Using a mechanistic static model based on clarithromycin inhibitory kinetic parameters derived from multiple in vitro studies employing non-statin probes, it has recently been estimated that inhibition of CYP3A4 represents the primary mechanism of clarithromycin’s interaction with simvastatin (36) (see discussion for further details).

**Impact of clarithromycin on the clinical pharmacokinetics (AUC and Cmax) of statins in humans**

The pharmacokinetic impact of concurrent administration of clarithromycin and statins has been investigated in five studies involving healthy subjects, see Table 2 (37–41). Overall, clarithromycin was found to increase systemic exposure to simvastatin markedly (up to 10-fold increase in AUC) and slightly to moderately increase systemic exposure to pravastatin and atorvastatin (AUC increases of 2-fold and 2-4-fold, respectively).

**Case reports**

Sixteen cases of suspected adverse drugs reactions, all involving rhabdomyolysis (42–55) (n = 14, including one with fatal outcome (50)) or less severe clinical myopathy (n = 2) (56,57), have been reported following concurrent use of clarithromycin (total daily dose range 250-1000 mg) with atorvastatin (n = 3, dose range 10-40 mg daily) (42–44), lovastatin (n = 2, both 40 mg daily) (45,46) or simvastatin (n = 11, dose range 20-80 mg daily) (47–57). The time-period from start of clarithromycin treatment to diagnosis of skeletal muscle toxicity ranged from 2-35 days. Aside from infection, background use of additional CYP3A4 inhibitor drugs is described in several of the cases as a potential contributory factor to the adverse event. For further details, see Supplementary Table.

**Risk of statin-related adverse events following co-prescription of statins with clarithromycin: observational studies**

Two Canadian population-based retrospective cohort studies examined statin-macrolide drug interactions (11,12). These studies found that co-prescription of clarithromycin with a statin that was metabolized by CYP3A4 and (11) /or (12) that was an OATP substrate increased the risk of
statin toxicity. Hence, the first study reported an increased 30-day risk of hospitalization with rhabdomyolysis (adjusted relative risk (RR) 2.17, 95% confidence interval (CI) 1.04-4.53), acute kidney injury (RR 1.78, 95% CI 1.49-2.14) and all-cause mortality (RR 1.56, 95% CI 1.36-1.80) among patients aged over 65 years who received a CYP3A4-metabolized statin (atorvastatin, simvastatin or lovastatin) concomitantly with clarithromycin or erythromycin as compared with azithromycin co-prescription (azithromycin does not, in contrast to clarithromycin and erythromycin, inhibit CYP3A4 or OATPs). The risk increase in absolute terms was, however, small (absolute risk difference 0.02%, 1.26% and 0.25%, respectively) (11). The predominant statin used in this population was atorvastatin (73%) followed by simvastatin (24%) and lovastatin (3%) (11). In the second study, compared with concurrent statin and azithromycin treatment, elderly patients prescribed clarithromycin while taking the non-CYP3A4 metabolized statins rosuvastatin (76%), pravastatin (21%) or fluvastatin (3%) (all OATP substrates) tended to have a similar 2-fold increased risk of hospitalization with rhabdomyolysis (adjusted RR 2.27, 95% CI 0.86-5.96) and also had increased risk of admission with acute kidney injury (adjusted RR 1.65, 95% CI 1.31-2.09) and hyperkalaemia (adjusted RR 2.17, 95% CI 1.22-3.86) together with increased all-cause mortality (adjusted RR 1.43, 95% CI 1.15-1.76) within 30 days of co-prescription. Again, the absolute risk increases were small, estimated at < 1% for each outcome (12).

A cohort study by Mesgrapour et al. (58) investigated, via Austrian health claims data, whether concomitant use of a statin (simvastatin, atorvastatin, pravastatin, lovastatin) with clarithromycin was associated with increased risk of hospitalization or death (composite outcome) as compared to - in a choice of questionable methodology - clarithromycin use in a cohort of patients who were not exposed to statins. Co-administration of a statin and clarithromycin was associated with a statistically significant increase in risk of hospitalization or death (RR 2.11, 95% CI 1.79-2.48). However, multivariate analysis was reported to show that age, cardiovascular disease, diabetes and utilization of other antibiotics fully explained this effect (multivariate corrected RR 1.02, 95% CI 0.85-1.22) (58).

Our literature search revealed an additional two observational studies examining the clinical relevance of exposure to CYP3A4-metabolized statins during concomitant use of a CYP3A4 inhibitor (including clarithromycin) (59,60). These studies did not stratify exposure to individual
CYP3A4 inhibitor drugs and, hence, did not specifically examine the interaction potential between clarithromycin and statins.

**Discussion**

Current product labelling for CYP3A4-metabolized statins states that co-administration of clarithromycin with either simvastatin or lovastatin is contraindicated and warns against exceeding a dose of 20 mg daily for atorvastatin when used in combination with clarithromycin (61–63). Nonetheless, use of such relatively or absolutely contraindicated drug combinations still occur, potentially subjecting patients to increased serum statin concentrations and risk of severe adverse drug reactions (ADRs). For example, in a population of 546 hospitalized Swiss patients given courses of clarithromycin or erythromycin, 31 patients were exposed to co-administrations of either simvastatin or ≥40 mg atorvastatin daily (64). According to observational studies, the absolute increase in risk of rhabdomyolysis and other serious ADRs associated with such co-treatment is small (< 1%) (11,12). However, the high prevalence of statin and macrolide utilization with subsequent potential for overlapping use between statins and clarithromycin creates a situation in which the absolute number of adverse events may be substantial. Hence, improved awareness and clinical handling of such DDIs is important.

Our literature search revealed pharmacokinetic (PK) studies of the effect of clarithromycin on three statins (Table 2). Hence, clarithromycin substantially increased systemic exposure to simvastatin (approximately 10-fold increase in AUC), and slightly to moderately increased AUCs of pravastatin and atorvastatin (increases of up to ≈2-fold and 4-fold, respectively). When considering the known critical disposition pathways governing the pharmacokinetics of each agent (Figure 1), the magnitudes of these AUC changes are in accordance with the mechanisms through which a perpetrator drug is generally thought to increase statin exposure, namely inhibition of CYP enzymes (most importantly CYP3A4), and/or inhibition of membrane statin transporters (notably OATB1B1) (13): simvastatin and, to a lesser extent, atorvastatin, are metabolized by CYP3A4, with both noted drugs being substrates of OATP1B1, while clarithromycin’s inhibition of the latter likely mediates the modest increase in exposure to pravastatin, which (like rosuvastatin and pitavastatin) is mainly excreted in unchanged form. As
per previously reported results, clarithromycin – and erythromycin/roxithromycin but not azithromycin – is an *in vitro* inhibitor of OATP1B1 and OATP1B3 (mechanism unknown) (32).

Clarithromycin contains a 14-membered macrocyclic lactone ring, as do the alternative macrolides erythromycin and roxithromycin. In contrast, azithromycin contains a 15-membered macrocyclic ring (due to addition of a methyl-substituted nitrogen atom) (65,66). CYP3A4 demethylates the macrolides to nitrosoalkenes, which may then form stable, inactive metabolite complexes with the enzyme. The process, known as mechanism-based inhibition (MBI), is irreversible and requires *de novo* synthesis of CYP enzyme before activity is restored. Compared with reversible drug-induced CYP inhibition, MBI more often causes serious DDIs and sustained duration of the interaction after discontinuation of the perpetrator drug. Published mean CYP3A4 turnover half-life values are highly variable, ranging from 10 to 140 hours (67). Using the highest estimate, recovery of full CYP34A activity may therefore take up to 23-29 days (4-5 turnover half-lives) after complete inhibition. To our knowledge, clinical studies are lacking on the duration of the interaction between any statin and clarithromycin (or other macrolides) following discontinuation of the antibiotic. Taking into account the half-lives of 5-6 hours of clarithromycin and its active 14-hydroxy metabolite (68), recovery of >75% of basal CYP3A4 enzyme level would be expected after 14 days even at a CYP3A4 turnover half-life of 140 hours. The degree of MBI varies among the macrolides with clarithromycin and erythromycin being most potent (69–72). Compared with the other macrolides, azithromycin is a weak inhibitor of CYP3A4, and it is not expected to alter the pharmacokinetics of statins that are primarily metabolized by CYP3A4 (simvastatin, lovastatin and atorvastatin) substantially/clinically. In contrast to its potent inhibition of CYP3A4, clarithromycin does not appear to affect the catalytic activity of CYP2C9 (73), the main CYP enzyme involved in oxidative metabolism of fluvastatin, suggesting that combining this statin with clarithromycin might be a safe alternative.

Based upon the *in vitro* data discussed above, clarithromycin’s interaction potential with lovastatin, pitavastin, rosuvastatin and fluvastatin may be inferred from PK studies involving erythromycin and the noted statins. Erythromycin 500 mg three-four times daily for 6-7 days markedly increased lovastatin exposure (≈ 6-fold increase in AUC) (74), moderately increased exposure to pitavastatin (nearly 3-fold AUC increase) (75) but was associated with a 20%
decrease in rosuvastatin AUC (76); in a single-dose study, erythromycin 500 mg did not significantly affect steady-state plasma concentrations of fluvastatin (77). Extrapolating from these results, it may be expected that rosuvastatin and fluvastatin are safe alternatives during co-treatment with clarithromycin. Tempering this assumption, however, is the retrospective cohort study by Li et al. (12), which as detailed in the results section reported that co-administration of clarithromycin with rosuvastatin, pravastatin or fluvastatin – as compared to azithromycin-statin co-administration - was associated with modest increases in the relative risk of several serious adverse outcomes compatible with statin-related adverse events. Future research, including multiple-dose PK studies, is needed to clarify the interaction potential between clarithromycin and the noted non-CYP3A4-metabolized statins.

Judged by the presented in vitro data and observational study results, azithromycin, a macrolide with indications, clinical use patterns and spectrum of activity similar (but not identical) to those of clarithromycin (75), may be considered as an alternative antibiotic in users of CYP3A4-metabolized statins. Nonetheless, some caution appears warranted: at least two published case reports (78,79) and a study of the World Health Organization (WHO) Adverse Drug Reaction database (80) have suggested an interaction between azithromycin and statins that are substrates of CYP3A4. The first case report describes a 51-year-old male patient using lovastatin (together with other regular medications, including the CYP3A4 inhibitor diltiazem), who developed rhabdomyolysis one day after finishing a 5-day course of azithromycin (78). In the second case, an increase in simvastatin dose from 40 to 80 mg and recent initiation of azithromycin together with nefazodone (CYP3A4 inhibitor) were possible contributing factors to rhabdomyolysis in a 56-year-old male patient (79). In the review of the WHO database, a disproportionality analysis found the observed number of rhabdomyolysis cases reported for azithromycin together with atorvastatin (n = 24), simvastatin (n = 20) or lovastatin (n = 5) to be two to three times greater than those expected (80). To our knowledge, PK investigations of the effect of azithromycin on statin exposure are limited to a single study, in which azithromycin 500 mg once daily for three days did not alter the steady-state pharmacokinetics of atorvastatin (40). Furthermore, it should be noted that, compared to clarithromycin, use of azithromycin has been reported to carry an increased risk of macrolide resistance, perhaps due to its much longer half-life (81).
In conclusion, we have presented the available evidence of DDIs between clarithromycin and statins. Balancing in vitro and clinical evidence of the interaction potential of clarithromycin with individual statins and extrapolating from data pertaining to the related macrolide erythromycin, we suggest the following strategies for managing statin and clarithromycin DDIs:

1) Atorvastatin, lovastatin and simvastatin: avoid co-administration with clarithromycin. If clarithromycin is necessary, withhold the statin for the duration of antibiotic treatment and for two weeks after clarithromycin is discontinued. Use of a non-macrolide antibiotic or use of azithromycin with caution may be considered.

2) Pitavastatin: If clarithromycin is necessary, consider withholding or dose-reducing pitavastatin for the duration of antibiotic treatment and for two weeks after clarithromycin is discontinued. Use of an alternative antibiotic, e.g. azithromycin, may be considered.

3) Pravastatin: If clarithromycin is necessary, continue statin therapy with caution, limiting pravastatin dose to 40 mg daily for the duration of antibiotic treatment and for two weeks after clarithromycin is discontinued. Use of an alternative antibiotic, e.g. azithromycin, may be considered.

4) Fluvastatin and rosvastatin: continue statin therapy with caution.

In the future, decision support systems may facilitate more precise clinical recommendations by integrating individual genetic and clinical risk factors (e.g. SLCO1B1 genotype, age, co-medication, statin dose).
References


Figure 1.
Records identified through database searches \((n=321)\)

Additional records identified through other sources \((n=4)\)

Records after duplicates removed \((n=283)\)

Records screened \((n=283)\)

Records excluded \((n=238)\)
\((156\text{ (title)} + 82\text{ (abstract)})\)

Full-text articles assessed for eligibility \((n=45)\)

Full-text articles excluded \((n=16)\)

Studies included \((n=29)\)

\[ \begin{align*}
\text{In vitro} & \quad (n=3) \\
\text{PK} & \quad (n=5) \\
\text{PD} & \quad (n=5) \\
\text{Case reports} & \quad (n=16)
\end{align*} \]
### Table 1. *In vitro* evidence of drug-drug interactions between clarithromycin and statins

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Expression system</th>
<th>Probe Substrate</th>
<th>Clarithromycin (µM)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>[I]&lt;sub&gt;1&lt;/sub&gt;/IC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>R-value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>OATP1B1</td>
<td>HEK293</td>
<td>Pravastatin (50)</td>
<td>10 + 100.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>(32)</td>
</tr>
<tr>
<td>OATP1B3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OATP1B1</td>
<td>MDCKII</td>
<td>Pitavastatin (0,1)</td>
<td>NR</td>
<td>26,2</td>
<td>0.12</td>
<td>1.98</td>
<td>(33)</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>HEK293</td>
<td>Atorvastatin (0,3)</td>
<td>0.03-1000</td>
<td>5.1 (OATP1B1)</td>
<td>0.61 (OATP1B1)</td>
<td>6.2 (OATP1B1)</td>
<td>(34)</td>
</tr>
<tr>
<td>OATP1B3</td>
<td></td>
<td></td>
<td></td>
<td>9.8 (OATP1B3)</td>
<td>0.32 (OATP1B3)</td>
<td>3.7 (OATP1B3)</td>
<td></td>
</tr>
</tbody>
</table>

HEK293, Human embryonic kidney cells; [I]<sub>1</sub>, mean steady state total (free and bound) C<sub>max</sub> following administration of highest proposed clinical dose of inhibitor (3.12 µM following clarithromycin 500 mg twice a day for 7 days), was derived from (82)*; IC<sub>50</sub>, half-maximal inhibitory concentration; MDCKII, Madin-Darby Canine Kidney cells; NR, not reported; OATP, organic anion-transporting polypeptide; R-values, the predicted ratios of the statins’ AUC (area under the plasma concentration time curve) in the presence and absence of clarithromycin, were calculated according to (35), with dose of clarithromycin set at 500 mg b.i.d. in (33) and 500 mg once daily in (34).
Table 2. *In vivo* studies of the effect of clarithromycin on statin pharmacokinetics

<table>
<thead>
<tr>
<th>Study design</th>
<th>N</th>
<th>Clarithromycin dose</th>
<th>Statin + statin dose</th>
<th>Change in statin AUC</th>
<th>Change in statin C\textsubscript{max}</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open-label, non-randomized, repeated dose.</td>
<td>12</td>
<td>500 mg twice daily for 7 days.</td>
<td>Simvastatin 40 mg single dose.</td>
<td>7.9-fold increase (from 33 to 230 ng·h·mL\textsuperscript{-1}).</td>
<td>8.2-fold increase (from 8.1 to 57.7 ng/mL).</td>
<td>(37)</td>
</tr>
<tr>
<td>Open-label, non-randomized, repeated dose.</td>
<td>8</td>
<td>250 mg daily for 7 days.</td>
<td>Simvastatin 20 mg daily for 7 days.</td>
<td>3.9-fold increase (from 15.1 to 58.5 ng·h·mL\textsuperscript{-1}).</td>
<td>2.3-fold increase (from 2.5 to 5.7 ng/mL).</td>
<td>(38)</td>
</tr>
<tr>
<td>Open-label, 2 phases, participants stratified according to CYP3A5*1 allele status.</td>
<td>23</td>
<td>500 mg twice daily for 5 days.</td>
<td>Atorvastatin 20 mg single dose.</td>
<td>2.6-fold increase in CYP3A5 non-expressors (n = 13, from 38.6 to 118.7 ng·h·mL\textsuperscript{-1}); 2.7-fold increase in CYP3A5 expressors (n = 10, from 40.7 to 102.4 ng·h·mL\textsuperscript{-1}).</td>
<td>P = ns for between-group difference.</td>
<td>(39)</td>
</tr>
<tr>
<td>Open-label, randomized, repeated dose.</td>
<td>36</td>
<td>500 mg daily for 3 days.</td>
<td>Atorvastatin 10 mg daily for 10 days.</td>
<td>1.8-fold increase (from 83.3 to 151.5 ng·h·mL\textsuperscript{-1}).</td>
<td>1.6-fold increase (from 8 to 12.5 ng/mL).</td>
<td>(40)</td>
</tr>
<tr>
<td>Open-label, randomized, repeated</td>
<td>45</td>
<td>500 mg twice daily for 8 days.</td>
<td>Simvastatin 40 mg daily, atorvastatin 80 mg daily</td>
<td>AUC\textsubscript{SIM}: 10-fold increase (from 22 to 219 ng·h·mL\textsuperscript{-1}); C\textsubscript{max, SIM}: 7-fold increase (from 7 to 50 ng/mL);</td>
<td></td>
<td>(41)</td>
</tr>
<tr>
<td>dose.</td>
<td>or pravastatin 40 mg daily for 8 days.</td>
<td>( \text{AUC}<em>{\text{ATOR}} ): 4.5-fold increase (from 102 to 454 ng·h·mL(^{-1} )); ( \text{AUC}</em>{\text{PRAV}} ): 2-fold increase (from 54 to 114 ng·h·mL(^{-1} )).</td>
<td>( C_{\text{max,ATOR}} ): 5-fold increase (from 21 to 113 ng/mL); ( C_{\text{max,PRAV}} ): 2-fold increase (from 18 to 41 ng/mL).</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ATOR, atorvastatin; AUC, area under the plasma concentration-time curve; \( C_{\text{max}} \), maximum plasma concentration; N = number of study subjects; ns = not significant; PRAV, pravastatin; SIM, simvastatin.