

Drug interactions with statins

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The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are generally well tolerated as monotherapy. Statins are associated with two important adverse effects, asymptomatic elevation in liver enzymes and myopathy. Myopathy is most likely to occur when statins are administered with other drugs. Statins are substrates of multiple drug transporters (including OAT-P1B1, BCRP and MDR1) and several cytochrome P450 (CYP) enzymes (including CYP3A4, CYP2C8, CYP2C19, and CYP2C9). Possible adverse effects of statins can occur due to interactions in concomitant use of drugs that substantially inhibit or induce their metabolic pathway. This review summarizes the most important interactions of statins.

Keywords: statins, drug interactions, cytochrome P450 (CYP) enzymes, drug transporters, adverse effects

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All important drug interactions, with the possible exception of idiosyncratic or allergic reactions, have a pharmacokinetic or pharmacodynamic basis, or both (1). A study of the mechanisms of drug interactions is of much value in selecting proper drug combinations in order to provide rational therapy, especially for drugs that have a narrow margin of safety and where drugs are used for a prolonged period of time. Most recently, pharmacogenetics has linked drug interaction outcomes to variations in genes encoding cytochrome P450 (CYP) enzymes (2) and transporter genes.

Statins (or HMG-CoA reductase inhibitors) represent a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. As of 2010, a number of statins have been on the market: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin (3).

Statins are associated with two uncommon, but important, adverse effects, asymptomatic elevation in liver enzyme activity and myopathy. In 2001, cerivastatin was withdrawn from the market worldwide because of an unacceptably high incidence of serious

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myopathy (creatine kinase >10 times the upper limit of normal) and rhabdomyolysis. Although rare, myopathy and rhabdomyolysis remain a serious concern with other statins as well (4, 5). Myopathy is most likely to occur when statins are administered with other drugs or chemicals that are themselves myotoxic or that can elevate statin concentrations to a toxic range. The mechanism of rhabdomyolysis caused by statins is poorly defined, but its occurrence increases with the drug dose/concentration (6). Therefore, the risk of adverse effects increases when drugs that can exclusively cause rhabdomyolysis are used concomitantly with other drugs that can increase their effects *via* interactions.

At the pharmacodynamic level (*i.e.*, at their site of action), statins are not prone to interfere with other drugs. However, at the pharmacokinetic level (*i.e.*, absorption, distribution, metabolism and excretion of a given drug), the available statins show notable differences, including half-life, systemic exposure, maximum plasma concentration (C_{\max}), bioavailability, protein binding, lipophilicity, metabolism, presence of active metabolites, and excretion routes (7, 8). Pharmacokinetic differences among statins are presented in Table I (9).

Table I. Clinical pharmacokinetics of statins (adapted from ref. 9)

Statin	t_{\max} (h)	C_{\max} (ng mL ⁻¹)	Bioavail- ability (%)	Lipo- philicity	Protein binding	Metabolism	Half-life (h)
Atorvastatin	2–3	27–66	12	Yes	80–90	CYP3A4	15–30
Fluvastatin	0.5–1	448	19–29	Yes	> 90	CYP2C9	0.5–2.3
Lovastatin	2–4	10–20	5	Yes	> 95	CYP3A4	1.3–2.8
Pravastatin	0.9–1.6	45–55	18	No	43–55	Sulphation	1.3–2.8
Rosuvastatin	3	37	20	No	88	CYP2C9, 2C19 (minor)	20.8
Simvastatin	1.3–2.4	10–34	5	Yes	94–98	CYP3A4	2–3

STATINS AS SUBSTRATES FOR CYP ENZYMES AND DRUG TRANSPORTERS

Statins are substrates for multiple membrane transporters including organic anion-transporting polypeptide (OATP1B1), breast cancer resistance protein (BCRP), and P-glycoprotein 1 (permeability glycoprotein, abbreviated as P-gp or Pgp) also known as multidrug resistance protein 1 (MDR1) and several cytochrome P450 (CYP) enzymes (including CYP3A4, CYP2C8, CYP2C19, and CYP2C9) (10). Drug transporters play an important role in statin disposition. Influx transporters, such as OATP1B1, and efflux transporters, such as multidrug resistance-associated protein 2 (MRP2), work together within the liver transcellular transport.

The significance of OATP1B1 has recently been emphasized by its inclusion among the seven transporters of considerable importance for drug disposition (11, 12). OATP1B1 transporter has been reported to be involved in the hepatic uptake of statins

and thus to reduce drug loss in systemic circulation and the development of side effects such as muscle myopathy. The gene encoding OATP1B1 is SLCO1B1. Clinical studies identified SLCO1B1 variants as a risk factor for statin-induced adverse events (13–15).

Genetic polymorphisms in SLCO1B1 affect the pharmacokinetics of statins. T521C and A388G are functional variants associated with Val174Ala and Asn130Asp. Two common full (SNPs) in SLCO1B1 have been associated with increased levels of pravastatin (16, 17). Also, a polymorphism in the 5'-untranslated region of SLCO1B1 affected the AUC and C_{\max} of pravastatin (18). A recent study examining the relationship between an OATP1B1 variant and atorvastatin and pravastatin-induced rhabdomyolysis found that the OATP-C*15 mutant allele was significantly higher in patients who experienced statin-induced myopathy, suggesting the significance of OATP1B1 down-regulation to statin exposure (19, 20). Thus, recent evidence demonstrated a significant difference in statin therapy outcomes, which could be, at least partially, attributed to the genetic variations of membrane transporters.

The liver biotransforms all statins, which accounts for their overall low systemic bioavailability. With the exception of pravastatin, which is transformed enzymatically in the liver cytosol, all statins undergo extensive microsomal metabolism by the cytochrome P450 (CYP) isoenzyme systems. Involvement of individual CYP enzymes or transporters in their disposition varies from statin to statin. The CYP3A4 isoenzyme is responsible for the metabolism of lovastatin, simvastatin, and atorvastatin. Fluvastatin is primarily metabolized by the CYP2C9 enzyme, with CYP3A4 and CYP2C8 contributing to a lesser extent (7). Rosuvastatin is not extensively metabolized, but has some interaction with the CYP2C9 enzyme (8).

Induction or inhibition of CYP450 isoenzymes is an important cause of drug interactions. Competitive inhibition between drugs at the enzymatic level is common and may serve to alter the disposition of statins, leading to increased plasma levels and greater risk of adverse events. On the basis of the above mentioned facts, it can be concluded that in patients requiring concurrent use of statins and CYP3A4 inhibitors, pravastatin or fluvastatin would be reasonable choices to minimize potential drug-drug interactions, whereas atorvastatin seems to carry a moderate risk and should be used with caution. Simvastatin and lovastatin carry the highest risk of drug interactions and should be avoided in patients taking concomitant CYP3A4 inhibitors (21).

Therefore, statin plasma levels may increase after CYP3A4 inhibitor treatments (10, 22) or get decreased by CYP3A4 inducers (23).

Major statin-drug interactions

Amiodarone. – Amiodarone is an antiarrhythmic agent used for various types of cardiac dysrhythmias and is a potent inhibitor of CYP3A4 (24, 25). This inhibition is primarily due to its active metabolite, desethylamiodarone, which noncompetitively inhibits CYP3A4 (26) and drugs metabolized by it, including statins. In previously reported cases, amiodarone was found to increase rhabdomyolysis risk when taken with simvastatin (21, 27–29). Simvastatin-related adverse event reports with concomitant amiodarone use were 1 %. The adverse event reports with atorvastatin and pravastatin use were 0.7 and 0.4 %, respectively, when combined with amiodarone, of which about 77 % were due to muscle toxicity (30). A study (31) revealed that 79 (85.9 %) patients on a combina-

tion of amiodarone and simvastatin at doses greater than 20 mg per day had at least one additional risk factor for myopathy or rhabdomyolysis during the history of combination therapy. Amiodarone-lovastatin co-administration also needs precaution because lovastatin is metabolized by CYP3A4 as well.

Antibiotics. – The macrolide antibiotics erythromycin, clarithromycin, troleandomycin, and telithromycin have been mentioned as potential interacting agents with statins in standard drug references (32) because they are cleared through the same metabolic pathway, regulated by CYP3A4. Even though the newer macrolide azithromycin has not been suggested to cause clinically significant interactions with agents metabolized through the cytochrome P450 enzyme system (33–35), there are certain case reports suggesting an interaction between azithromycin and statins (36–38).

Even though the major mechanism underlying drug interactions with macrolides is believed to be inhibition of the major drug metabolizing enzyme CYP3A4 in small intestine and liver, published data indicate that certain macrolides are also inhibitors of the apically/luminally localized drug efflux pump P-gp (39–41). By inhibiting P-gp function they increase drug absorption from the gut lumen and decrease biliary elimination and renal secretion of concomitantly administered drugs (42). This in turn leads to increased drug concentrations and drug toxicity. It has been demonstrated that the macrolides clarithromycin and erythromycin significantly increase pravastatin plasma concentrations (43). Because pravastatin is not metabolized by cytochrome P450 enzymes, uptake transporters may account for this drug-drug interaction. Despite the increasingly recognized role of full OATP uptake transporters in drug disposition, their role has not been systematically studied. However, macrolides are inhibitors of the uptake of concomitantly administered drugs mediated by OATPs and thereby provide an additional mechanism of macrolide-induced drug interactions (44). Hirano *et al.* (45) recently demonstrated that both clarithromycin and erythromycin were inhibitors of the uptake of pitavastatin, an established OATP1B1 substrate.

Among fluoroquinolone antibiotics, fluoroquinolone ciprofloxacin is partially metabolized in liver. It is a strong inhibitor of CYP1A2 and a weak inhibitor of CYP3A4. Ciprofloxacin-simvastatin interaction has been reported to the Medicines and Healthcare Products Regulatory Agency (MHRA), UK (46).

Azole antifungals. – Co-administration of simvastatin with itraconazole, an antifungal agent, can result in rhabdomyolysis (47). Itraconazole, even at a small dosage of 100 mg daily, greatly elevated plasma concentrations of lovastatin and its active metabolite, lovastatin acid. Therefore, lovastatin should not be used concomitantly with itraconazole and other potent CYP3A4 inhibitors, or the dosage of lovastatin should be greatly reduced while using a CYP3A4 inhibitor. In contrast, fluvastatin concentration was not significantly increased by itraconazole, indicating that fluvastatin has much less potential than lovastatin for clinically significant interactions with itraconazole (48). Interactions between ketokonazole and simvastatin (49–51) or lovastatin (52) have also been described. Rhabdomyolysis as a consequence of fluconazole interaction with statins has been reported as well (53–56).

Calcium channel antagonists. – Calcium channel antagonists are weak inhibitors of CYP3A4. They increase the plasma concentration of statins (57, 58). Both benidipine and

azelnidipine have been shown to inhibit metabolism *in vitro* in a concentration-dependent manner (59).

Cases of rhabdomyolysis have been reported with the association of diltiazem with atorvastatin or simvastatin (60, 61), suggesting some need for caution in using these agents simultaneously.

Mibefradil, at therapeutically relevant concentrations, strongly suppressed the metabolism of simvastatin, lovastatin, atorvastatin and cerivastatin in human liver microsomes through its inhibitory effects on CYP3A4/5, while the effects of mibefradil on fluvastatin, a substrate for CYP2C8/9, were minimal in this system (62).

Administration of nifedipine may elicit a detrimental effect on statin therapy, resulting in a worsening of cardiac performance. This may suggest another mechanism of drug-drug interaction than the one based on CYP3A4 inhibition (63).

The effects of verapamil on the pharmacokinetics of simvastatin and lovastatin have been investigated in healthy volunteers. Verapamil caused a 4.6-fold increase in the mean area under the concentration-time curve of simvastatin (64).

Citrus juices. – Given that simvastatin, lovastatin and atorvastatin are metabolized by CYP3A4, they are affected by the interaction with grapefruit juice, which has been reported to inhibit CYP3A4. However, a number of studies focus on other interaction mechanisms besides that of CYP 3A4. Grapefruit juice also inhibits P-gp, a transporter that carries drugs from the enterocyte back to the gut lumen, resulting in further increase in the fraction of the drug absorbed. Grapefruit juice is also capable to inhibit human organic anion-transporting polypeptide B (OATP-B) *in vitro* (65). This inhibition decreases the intestinal uptake and therefore the oral bioavailability of the drug, which is the opposite effect to that of CYP3A4 inhibition. Nevertheless, the contribution to the bioavailability of statins affected by P-gp and OATP-B inhibition remains unclear. In 2007, esterase inhibition by grapefruit juice was described as a new drug interaction (66).

Remarkably, even one glass of grapefruit juice taken daily considerably increases plasma concentrations of simvastatin and simvastatin acid. Grapefruit juice may increase both the cholesterol-lowering effect and the risk of adverse effects of simvastatin (67, 68).

Lilja *et al.* (69) demonstrated that grapefruit juice significantly increases serum concentrations of atorvastatin, both in its acid and lactone forms. Nevertheless, this juice does not appear to have any effect on the pharmacokinetics of pravastatin due to its hydrosolubility (70). A Japanese study also confirmed the interaction of grapefruit juice with atorvastatin but not with pravastatin (71).

Orange juice increases pravastatin *AUC*, without affecting its excretion rate. This effect could be related to higher intestinal absorption of the drug, mediated by the orange juice, but the mechanism is not clear and further studies are necessary. Orange juice does not alter simvastatin pharmacokinetics (72). One report highlights the possible interaction between rosuvastatin and pomegranate juice that caused rhabdomyolysis in one patient (73).

Immunosuppressants. – Previous clinical studies have shown that plasma concentration of pitavastatin was increased by cyclosporine A (74). It has been demonstrated that OATP could be a major determinant of causing clinical drug-drug interactions between cerivastatin and cyclosporine as well (20, 75). The area under the curve of the OATP1B1

substrate rosuvastatin was increased 7.1 times when it was co-administered with the OATP1B1 inhibitor cyclosporine A. *In vitro* models suggested that the observed increase in the *AUC* was related to the inhibition of OATP1B1 (12, 76).

There are case reports of developing rhabdomyolysis due to concomitant use of simvastatin and cyclosporine (77–79). Fluvastatin, which is primarily metabolized by CYP2C9, and pravastatin and rosuvastatin, which are eliminated by other metabolic routes, are less subject to this interaction than other statins. However, a 5- to 23-fold increase in pravastatin bioavailability has been reported in the presence of cyclosporine A. This suggests that cyclosporine may interact with statins *via* mechanisms not limited to CYP3A4 inhibition. On the other hand, fluvastatin shows a far milder interaction with cyclosporine (7, 80).

An interaction between erlotinib and simvastatin leading to rhabdomyolysis has been reported (81). The results of a study by Katsakiori (82) empower the belief that tacrolimus and concomitantly administered statin do not interact in terms of efficacy, efficiency and side-effect development. No significant clinical interaction was observed even for atorvastatin and simvastatin.

Nefazodone. – Concurrent administration of nefazodone, an antidepressant, and an HMG-CoA reductase inhibitor metabolized by CYP3A4 may result in elevated statin levels. Elevated levels of the HMG CoA reductase inhibitor may result in rhabdomyolysis (83, 84). In a single-dose study, the administration of simvastatin (40 mg) or atorvastatin (40 mg) following six days of nefazodone (200 mg twice daily) resulted in a 20-fold increase in simvastatin and simvastatin acid levels and a 3- to 4-fold increase in atorvastatin and atorvastatin lactone levels (85).

Protease inhibitors. – A significant potential exists for drug-drug interactions with the combination of protease inhibitors and statins *via* competitive and reversible inhibition of CYP3A4. Certain agents of the HIV protease inhibitor class can induce elevations in serum lipids (86, 87).

Nelfinavir, 1250 mg twice daily taken with either atorvastatin (10 mg once daily) or simvastatin (20 mg once daily), caused a 74 % increase in the *AUC* of atorvastatin and 505 % increase in the *AUC* of simvastatin (88).

Co-administration of lopinavir-ritonavir with atorvastatin (20 mg once daily) caused a 5.8-fold increase in atorvastatin *AUC*, whereas lopinavir-ritonavir given with pravastatin (20 mg once daily) had relatively little effect on pravastatin (89).

A 40 mg dose of either simvastatin, atorvastatin or pravastatin was administered with the dual protease inhibitor regimen of saquinavir soft gel capsule 400 mg twice daily and ritonavir 400 mg twice daily. The combination had a dramatic impact on simvastatin, with the area under the curve of simvastatin acid, the active form of simvastatin, increasing by 3000 %. The *AUC* of total active atorvastatin (the sum of atorvastatin plus two active metabolites) increased by 79 % (90).

Surprisingly, the *AUC* of pravastatin decreased by 50 % in the presence of saquinavir plus ritonavir. In a separate study, nelfinavir given concomitantly with pravastatin caused a 47 % decrease in the *AUC* of pravastatin (91).

A clinically relevant increase in rosuvastatin and atorvastatin concentrations during co-administration of tipranavir co-administered with low-dose ritonavir (tipranavir/r)

500 mg/200 mg twice daily was reported. Based on these results, a low initial dose of rosuvastatin (5 mg) and atorvastatin (10 mg) is recommended when combined with tipranavir/r, with careful clinical monitoring of rosuvastatin- or atorvastatin-related adverse effects, such as myopathy (92).

Warfarin. – Although an interaction study has demonstrated a lack of interaction between atorvastatin and warfarin after 15 days of combination therapy (93), at least three studies have shown consistent increases in warfarin effect and/or dose reductions during concurrent use of simvastatin (94–96). A case of fatal cerebral hemorrhage following a switch from atorvastatin to simvastatin in a patient taking warfarin has been reported (97). Three reports described interactions between warfarin and lovastatin in which prothrombin times were increased (98–100). In addition, two reports (case series) of possible interactions with fluvastatin and warfarin cited three cases each (101, 102).

Phenytoin. – Phenytoin, another inducer of CYP3A4, can alter the lipid-lowering efficacy of both atorvastatin and simvastatin (103, 104).

Rifampicin. – It has been shown that rifampicin greatly decreases plasma concentrations of simvastatin (105). Rifampicin also caused a statistically significant decrease in the plasma concentration of pravastatin given as a single oral dose to healthy subjects. However, the effect of rifampicin varied greatly between subjects. The mean rifampicin-induced decrease in pravastatin concentration was considerably smaller than that observed previously for simvastatin (106).

St. John's wort. – The herbal supplement St. John's wort appears to decrease plasma levels of simvastatin but not those of pravastatin (107, 108).

Clopidogrel. – Previous studies suggested that atorvastatin, but not pravastatin, *in vitro* decreased the inhibitory effect of clopidogrel on platelet aggregation (109).

A population-based cohort study investigated interactions between CYP3A4-metabolized statins and clopidogrel (110). Compared to the control group (treated with non-CYP3A4-metabolized statins), co-prescription of CYP3A4-metabolized statins was associated with an increase in adverse outcomes, though not statistically significant. This controversy remains unresolved, since subsequent studies investigating the effects of atorvastatin and/or simvastatin on anti-platelet effects of clopidogrel failed to confirm the initial findings (110–116).

Other authors (117) have shown that at clopidogrel concentrations $> 10 \mu\text{mol L}^{-1}$, CYP3A4 is mainly responsible for clopidogrel biotransformation, whereas CYP2C19 contributes only at clopidogrel concentrations $\leq 10 \mu\text{mol L}^{-1}$, which may explain the conflicting results of *in vitro* and *in vivo* investigations regarding drug interactions with clopidogrel.

Fibrates. – The absence of a significant pharmacokinetic interaction between fenofibrate and atorvastatin is consistent with recent results showing no difference in the safety profile between atorvastatin used as monotherapy or in combination with fenofibric acid. Together, these data suggest that atorvastatin-fenofibrate combination therapy is unlikely to pose a risk to patients (118).

Reports on the *in vitro* inhibitory potential of gemfibrozil demonstrated that this lipid-lowering drug is a more potent inhibitor of CYP2C9 than of CYP2C8 (119–121).

However, in the clinic, gemfibrozil is a more potent inhibitor of CYP2C8 than of CYP2C9. Interaction between gemfibrozil and pravastatin could occur at the transport protein level. Gemfibrozil increases the *AUC* of the open acid form of simvastatin, lovastatin, pravastatin, and pitavastatin, but it does not affect the *AUC* of the lactone form of simvastatin and lovastatin and reduces that of pitavastatin (122–126). Gemfibrozil seems to have no effect on the plasma concentration of fluvastatin (127).

The limited effect of gemfibrozil on plasma concentrations of the open acid forms of simvastatin and lovastatin can be explained by inhibition of lactone formation followed by full (UGT)-mediated glucuronidation. The reduced *AUC* of the lactone form of pitavastatin may be also explained by the same mechanism (121).

In addition, the membrane transporter OATP1B1 may also be involved in the reported drug-drug interactions of gemfibrozil and a number of statins (10, 12). In the approved label of pravastatin, there is a statement on the risk of its co-administration with cyclosporine. The approved label of simvastatin also bears a statement on the risk of myopathy when it is co-administered with cyclosporine or gemfibrozil (both are OATP1B1 inhibitors) (15).

Digoxin. – Digoxin may affect the pharmacokinetics of statins. Acute interactions have been observed with simvastatin (128) and co-administration of atorvastatin 80 mg per day and digoxin 0.25 mg per day for 20 days increased systemic exposure to digoxin by inhibiting P-glycoprotein. However, administration of atorvastatin 10 mg per day with digoxin did not affect the mean steady-state concentrations of digoxin (129). Rosuvastatin, but not fluvastatin, has been shown to be recognized by these drug transporters (130, 131).

Major drug interactions with statins are presented in Table II.

Table II. Major drug interactions with statins and the proposed interaction mechanism

Mechanism of interaction	Drug/substance	Reference
Inhibition of CYP3A4	Amiodarone	21, 24–31
	Azithromycin	32–38
	Erythromycin	46
	Clarithromycin	
	Telithromycin	
	Troleandomycin	
	Ciprofloxacin	
	Itraconazole	47–56
	Ketokonazole	
	Fluconazole	
	Azelnidipine, benidipine	57–64
	Diltiazem	
	Mibefradil	
	Nifedipine	
Verapamil		

	Grapefruit juice	66–73
	Orange juice, pomegranate juice	
	Clopidogrel	109–117
	Cyclosporine	7, 77–80
	Erlotinib	81
	Tacrolimus	82
	Nefazodone	83–85
	Nelfinavir	86–92
	Lopinavir	
	Ritonavir	
	Saquinavir	
	Tipranavir	
	Warfarin	93–102
Induction of CYP3A4	Phenytoin	103, 104
	Rifampicin	105, 106
	St. John's wort	107, 108
Inhibition of CYP2C8 and CYP2C9	Gemfibrozil	118–127
Inhibition of CYP2C19	Clopidogrel	117
Inhibition of P-gp (MDR1)	Azithromycin	39–45
	Erythromycin	
	Clarithromycin	
	Telithromycin	
	Troleandomycin	
	Digoxin	128–131
Inhibition of OATP1B1	Citrus Juice	65
	Grapefruit juice	
	Orange juice, pomegranate juice	
	Cyclosporine	12, 20, 74–76
	Gemfibrozil	10, 12, 15

CONCLUSIONS

Drug-drug interactions are identified as a leading cause of hospitalization and death. However, it is unlikely that all clinically possible interactions can be predicted. Conditions under which drug-drug interactions occur, their clinical relevance, and mechanisms causing them, therefore represent a highly active field in pharmacological research. Statins have proven to be safe in numerous clinical trials. However, studies have shown that they can interact with other co-administered medicines. Principal mecha-

nisms of drug-drug interactions are a direct inhibition of enzymatic activity, which may be reversible or irreversible in nature, and induction or repression of enzyme gene expression. Furthermore, genetic variations of drug transporters appear to have an additional role in the fate of statins in human body. The different pharmacokinetic profiles of different statins should be carefully examined in order to understand the different spectra of drug interactions. These interactions are important determinants of safety in patients with hypercholesterolemia, especially those requiring long-term therapy with drugs that are well-known CYP3A4 inhibitors/inducers. Therefore, concern is warranted particularly when statins are used in the multidrug regimens due to the dose-dependent toxicity and their propensity toward marked elevations in concentration if taken with drugs that inhibit first-pass metabolism.

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