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Incidence of potential drug interactions in co-prescription of statins and macrolide antibiotics in Croatia during the 14 year period

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The objective of this study was to determine the number of patients on the national level that took macrolide antibiotics along with chronic statin therapy in Croatia in the period from 2002 to 2015, and to analyse prescription patterns. In 2002, statins were used in the treatment of 2.6% of the total number of insured persons in Croatia. By 2015, this number increased to 8.4%. In the period studied, on average 15.3% of the patients on statin therapy were co-prescribed macrolide antibiotics. Erythromycin was combined with different statins on average in 1.4% of cases, clarithromycin in 25.5% and azithromycin in 73.2% of the cases. Relative frequency of combining statins with macrolides was similar for all statins. On average, 11.5% of patients on concomitant statin-macrolide therapy were taking high-dose statins. On average, 90% of these co-prescriptions can lead to potentially clinically significant DDIs (X, D, C). The co-prescription of statins and macrolide antibiotics in the Republic of Croatia is increasing. The greatest number of co-prescriptions with macrolides were with atorvastatin and simvastatin.

1. Introduction

Macrolides are widely prescribed in community-based practice and are able to affect the biotransformation of most statins, thus increasing the blood concentration of statins. Simvastatin, lovastatin and atorvastatin are mostly metabolised by cytochrome P450 CYP3A4 isoenzymes; fluvastatin is metabolised by those isoenzymes to a much lesser extent, and pravastatin is not metabolized by this mechanism. Metabolism of rosuvastatin appears to be minimal and is principally mediated by the CYP2C9 enzyme, with little involvement of CYP3A4. Consequently, CYP3A4 inhibitor drugs are at interaction risk with simvastatin, lovastatin and atorvastatin, and much less with fluvastatin and pravastatin (Rowan et al. 2012).

Erythromycin, clarithromycin, and telithromycin are the most potent inhibitors of the CYP3A4 isoenzyme, followed by the weak inhibitor roxithromycin, and finally azithromycin, which in some studies showed results comparable to placebo (Greenblatt et al. 1998; Ito et al. 2003; Pinto et al. 2005; Polasek and Miners 2006). The other proposed mechanism of statin-macrolide interactions, especially with non-CYP3A4-dependent statins, is *via* inhibition of the SLCO1B1 (OATP1B1) uptake transporter by clarithromycin or erythromycin, leading to reduced hepatic uptake of the statin (Pasanen et al. 2006; Igel et al. 2006; Seithel et al. 2007; SEARCH Collaborative Group, 2008).

The mechanism by which azithromycin would interact with a statin is unclear, as azithromycin is generally not considered to be a significant inhibitor of CYP3A4-mediated metabolism or of SLCO1B1 (OATP1B1)-mediated statin uptake. But it should be emphasized that some case reports have described patients with rhabdomyolysis attributed to an interaction between azithromycin and statins (Grunden and Fisher 1997; Strandell et al. 2009; Alreja et al. 2012). Although this combination is generally considered to be of lower risk than combinations including clarithromycin or erythromycin, Lexi-Interact recommends extra caution when considering the use of azithromycin together with simvastatin, atorvastatin or lovastatin.

A lot of evidence indicates that the combined use of these two therapeutic groups implies a high risk of developing serious or even fatal adverse effects, e.g. rhabdomyolysis (Lee and Maddix 2001; Omar and Wilson 2002; Molden and Andersson 2007; Bouquie et al. 2011; Alreja et al. 2012; Fallah et al. 2013; Mesgarpour et al. 2015).

Table 1: Studied statin – macrolide combinations

Drug 1	Drug 2	Clinical significance group
Simvastatin	Erythromycin	X
	Clarithromycin	X
	Azithromycin	D
Lovastatin	Erythromycin	D
	Clarithromycin	D
	Azithromycin	D
Pravastatin	Erythromycin	D
	Clarithromycin	D
	Azithromycin	A
Fluvastatin	Erythromycin	C
	Clarithromycin	C
	Azithromycin	A
Atorvastatin	Erythromycin	D
	Clarithromycin	D
	Azithromycin	C
Rosuvastatin	Erythromycin	C
	Clarithromycin	C
	Azithromycin	A

Table 2: Total number of patients on statin therapy

Statin	Year													
	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Simvastatin	79,776	109,024	129,964	129,958	135,306	159,823	169,198	162,205	155,469	132,418	115,030	95,313	82,406	72,751
Lovastatin	6,217	3,562	2,591	1,681	1,381	1,293	950	779	678	131	0	0	0	0
Pravastatin	0	47	3,660	2,962	2,291	1,076	41	1	0	0	0	0	0	0
Fluvastatin	6,420	6,458	6,587	14,749	20,541	24,428	27,477	25,329	24,712	19,579	15,961	13,167	11,044	9,031
Atorvastatin	16,691	34,471	52,792	82,361	117,344	141,996	163,084	175,023	202,197	198,812	199,824	188,596	188,318	193,789
Rosuvastatin	0	0	0	0	0	0	0	0	13,079	36,474	57,844	74,203	84,125	89,616
Total	**109,104**	**153,562**	**195,594**	**231,711**	**276,863**	**328,616**	**360,750**	**363,337**	**396,135**	**387,414**	**388,659**	**371,279**	**365,893**	**365,187**

The aim of this study was to establish how many patients in Croatia concomitantly take statins with macrolides, and analyse co-prescription patterns.

2. Investigations, results and discussion

This retrospective study analysed all outpatients in Croatia on statin therapy which were dispensed a macrolide within 30 days of having been dispensed a statin. The objective was to analyse the incidence and relevance of potential statin-macrolide interactions. The study included all the population insured by CHIF (Croatian Health Insurance Fund for compulsory health insurance in the Republic of Croatia), and covered over 98% of the total population. CHIF handles the data on all reimbursed drugs dispensed to outpatients in pharmacies. In Croatia, statin drugs and macrolide antibiotics are issued exclusively on prescription.

Observed co-prescriptions of statins with macrolides are shown in Table 1. Interactions were identified using Lexi-Comp® Lexi-Interact™ Online (Lexi-Comp, Inc., Hudson, USA). This program categorizes interactions in five risk rating categories A, B, C, D and X. Categories C, D and X are considered to be clinically significant interactions.

Statins were used in the treatment of 2.6% of the total number of insured persons in Croatia in 2002. By 2015, this number increased to 8.3%. During the same period, macrolides were used in the treatment of, on average, 13.4% of the total number of insured persons in Croatia (Table 2, Fig. 1).

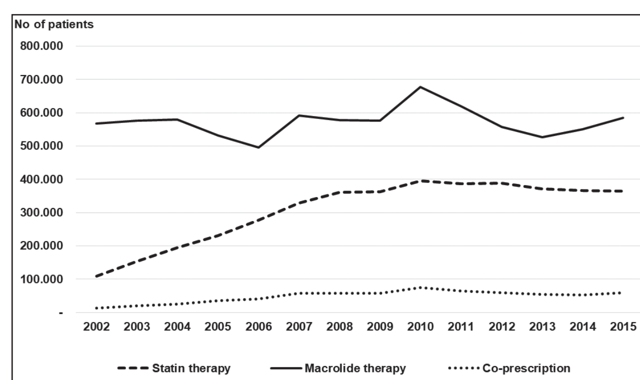


Fig. 1: Absolute number of patients on therapy

Previous studies have shown that 2.5 – 17.4% of patients on statin therapy were receiving macrolides (Table 3). In this study, 15.3% of patients on statin therapy were co-prescribed macrolide antibiotics. The rates in this study are significantly higher compared to the results of an earlier study by Reiner et al. who studied 882 patients taking statins during a one-year period, and found that 8% of them were receiving macrolides. Since Reiner's data also included Croatia in the period from 1 June 2003 to 1 June 2004, the difference can be attributed to a much smaller sample in this earlier study (882 vs. ~4,000.000 patients), and the fact that the data were collected from general practitioners' health records all over Croatia (Reiner et al. 2005).

In 2002, macrolides were co-prescribed to 12,593 patients on statin therapy which is 11.5% of all patients on statin therapy or 0.3% of the total number of insured persons in Croatia. By 2015, this number increased by 4.8 times (Fig. 1, Table 4). The number of patients with statin-macrolide co-prescriptions is growing proportionally with the number of patients on statin therapy.

Relative frequency of statin-macrolide co-prescription is similar for different statins and varies from 14.5% (lovastatin) to 18.2% (pravastatin) (Table 4). However, due to a much higher number of patients using simvastatin or atorvastatin rather than other statins, the absolute number of potentially clinically significant DDIs (drug-drug interactions) is much higher with these two drugs (Fig. 2, Table 4).

In the studied period, on average 43,138 potentially clinically significant interactions per year were identified: 17,893 C interactions (41.5%), 19,945 D interactions (46.2%) and 5,299 X interactions (12.3%). From 2002 to 2010 there was an increase, and from 2010 there was a decrease of statin-macrolide co-prescriptions which can lead to X and D interactions. This can be explained by the introduction of rosuvastatin to the Croatian market in 2010 and its increasing usage (Table 4, Figs. 3, 4).

As simvastatin, lovastatin and atorvastatin are predominantly metabolised by cytochrome P450 isoenzyme 3A4, serious adverse events can occur when these drugs are taken in combination with drugs competing as substrates, or inhibiting the isoenzyme CYP3A4. Due to the significantly increased concentration of statins in plasma, the possibility for dangerous DDIs is increased, which can lead to an increased risk for myopathy and rhabdomyolysis (Abu Mellal et al. 2019).

In our study, 26.8% of simvastatin-macrolide co-prescriptions can potentially lead to X interactions (simvastatin-erythromycin or

Table 3: Comparison of the results of different studies

Country	Croatia	Croatia	Italy	Ireland	U.S.A.	Canada	U.K.
Authors	**Reiner**	**Grgurević**	**Piancetini**	**Heerey**	**Stang**	**Einarson**	**Bakhai**
	et al.	**et al.**	**et al.**	**et al.**	**et al.**	**et al.**	**et al.**
Number of patients in study	882	avg 4,261,173	190,124	7,606	5,637,918	28,705	364,574
Number of patients on statin therapy	882	avg 306,722	7,176	7,606	5,637,918	28,705	364,574
Study period	1 year	14 years	1 year	1 year	1 year	3.25 years	1.25 year
Percentage of statin taking patients that were co-prescribed macrolides	8.0%	15.3%	3.2%	2.5%	17.5%	11.7%	5.8%

Table 4: Percentage of patients with a statin-macrolide co-prescriptions relative to the number of patients receiving the statin

Drug 1	Drug 2	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Simvastatin	Erythromycin	0.4	0.4	0.4	0.3	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1
Simvastatin	Clarithromycin	0.9	1.3	2.6	3.8	4.2	5.9	5.7	4.7	5.7	4.4	4.1	3.5	3.2	3.5
Simvastatin	Azithromycin	10.2	11.2	9.5	11.0	9.8	10.8	9.7	10.5	12.7	11.1	10.4	10.1	10.3	11.7
Simvastatin Total		11.5	12.9	12.5	15.1	14.3	16.9	15.6	15.3	18.5	15.6	14.6	13.7	13.7	15.4
Lovastatin	Erythromycin	0.4	0.3	0.4	0.4	0.1	0.2	0.2	0.4	0.2	0.0	0.0	0.0	0.0	0.0
Lovastatin	Clarithromycin	0.9	1.4	2.2	4.1	3.3	6.0	7.4	5.8	5.6	3.8	0.0	0.0	0.0	0.0
Lovastatin	Azithromycin	9.2	9.7	8.4	10.7	8.6	11.4	9.9	8.5	13.9	11.5	0.0	0.0	0.0	0.0
Lovastatin Total		10.4	11.4	11.0	15.2	12.1	17.5	17.5	14.6	19.6	15.3	0.0	0.0	0.0	0.0
Pravastatin	Erythromycin	0.0	0.0	0.5	0.2	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Pravastatin	Clarithromycin	0.0	0.0	3.5	4.2	4.8	6.5	14.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Pravastatin	Azithromycin	0.0	21.3	9.8	11.8	10.6	11.3	9.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Pravastatin Total		0.0	21.3	13.7	16.2	15.6	17.8	24.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Fluvastatin	Erythromycin	0.3	0.4	0.4	0.3	0.3	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1
Fluvastatin	Clarithromycin	1.0	1.6	2.9	4.3	4.4	6.4	5.9	5.0	5.8	4.4	4.1	3.4	3.5	3.4
Fluvastatin	Azithromycin	9.5	11.6	10.3	11.5	10.7	12.2	11.3	11.5	13.6	12.3	11.4	10.9	11.0	12.7
Fluvastatin Total		10.8	13.6	13.5	16.1	15.3	18.9	17.5	16.7	19.4	16.8	15.6	14.5	14.6	16.3
Atorvastatin	Erythromycin	0.4	0.4	0.4	0.3	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1
Atorvastatin	Clarithromycin	1.0	1.4	2.9	4.3	4.6	6.4	6.0	5.0	6.0	4.7	4.4	3.7	3.4	3.7
Atorvastatin	Azithromycin	11.0	12.9	10.8	12.0	10.6	11.3	10.5	11.0	13.2	11.8	11.0	10.5	10.7	12.4
Atorvastatin Total		12.4	14.7	14.0	16.5	15.5	17.9	16.7	16.1	19.4	16.6	15.4	14.3	14.1	16.2
Rosuvastatin	Erythromycin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.1	0.1	0.1	0.1	0.1
Rosuvastatin	Clarithromycin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.0	5.8	5.0	4.4	4.1	4.2
Rosuvastatin	Azithromycin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	14.9	13.2	12.1	11.5	11.8	13.5
Rosuvastatin Total		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	22.1	19.1	17.2	16.0	15.9	17.8
Statins Total		11.5	13.3	12.9	15.7	14.9	17.5	16.2	15.8	19.1	16.5	15.5	14.5	14.5	16.4

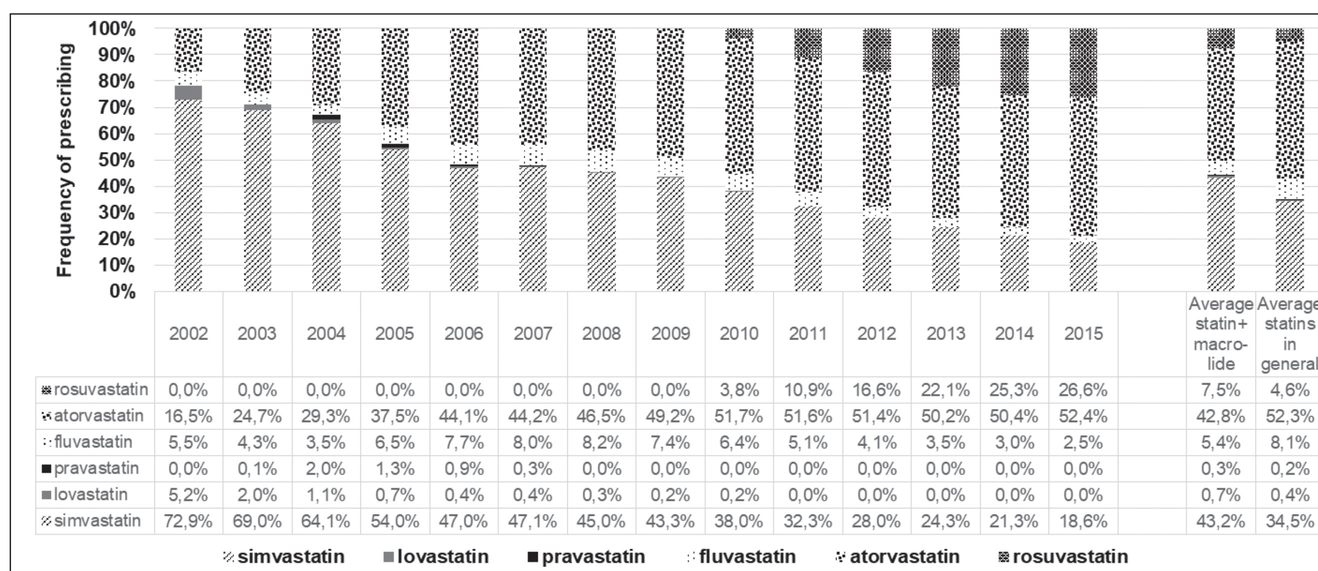
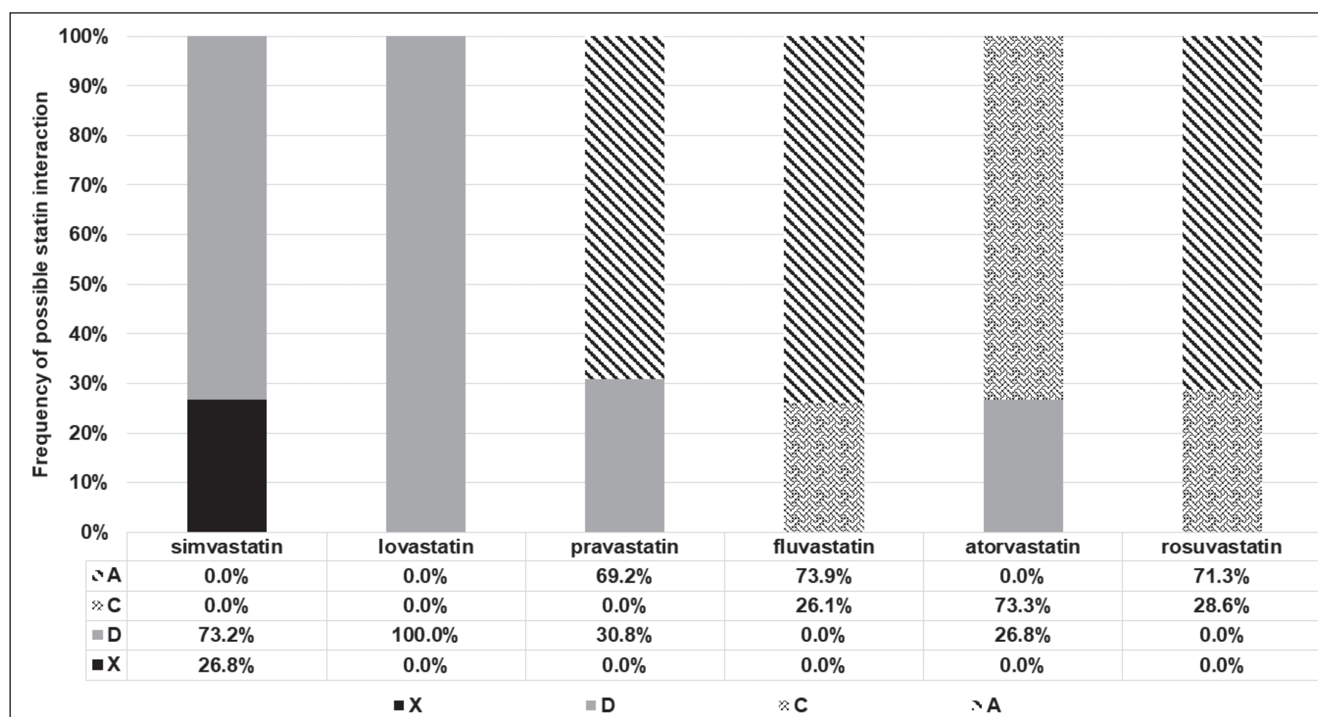


Fig. 2: Frequency of prescribing different statins with macrolide antibiotics

simvastatin-clarithromycin). On average, 5,299 patients per year were prescribed these drug combinations (Figs. 3, 4).

In the present study, 19,945 co-prescriptions can potentially lead to D interactions. In this category, there were 100% of lovastatin-macrolide co-prescriptions, on average 242 cases per year and 30.8% on pravastatin-macrolide co-prescriptions, on average 94 cases per year. The absolute number of cases was much higher in the atorvastatin and the simvastatin-macrolide co-prescriptions group. On average, 6,586 cases per year, i.e. 26.8% of atorvastatin-macrolide co-prescriptions and, on average, 13,153 cases per year, i.e. 73.2% of simvastatin-macrolide co-prescriptions required specific modification of therapy (Fig. 3).

From the macrolide perspective, erythromycin is co-prescribed with different statins, on average in 502 cases per year, or 1.4% of all statin-macrolide co-prescriptions. Clarithromycin is involved on average in 13,401 cases per year, or 25.5%, and azithromycin on average in 34,321 cases per year, i.e. 73.2% cases. This approximately corresponds to the proportions of different macrolides in the therapy of the entire population (Fig. 5).



	simvastatin	lovastatin	pravastatin	fluvastatin	atorvastatin	rosuvastatin
A	0.0%	0.0%	69.2%	73.9%	0.0%	71.3%
C	0.0%	0.0%	0.0%	26.1%	73.3%	28.6%
D	73.2%	100.0%	30.8%	0.0%	26.8%	0.0%
X	26.8%	0.0%	0.0%	0.0%	0.0%	0.0%

Fig. 3: Frequency of possible statin interactions by clinical significance group

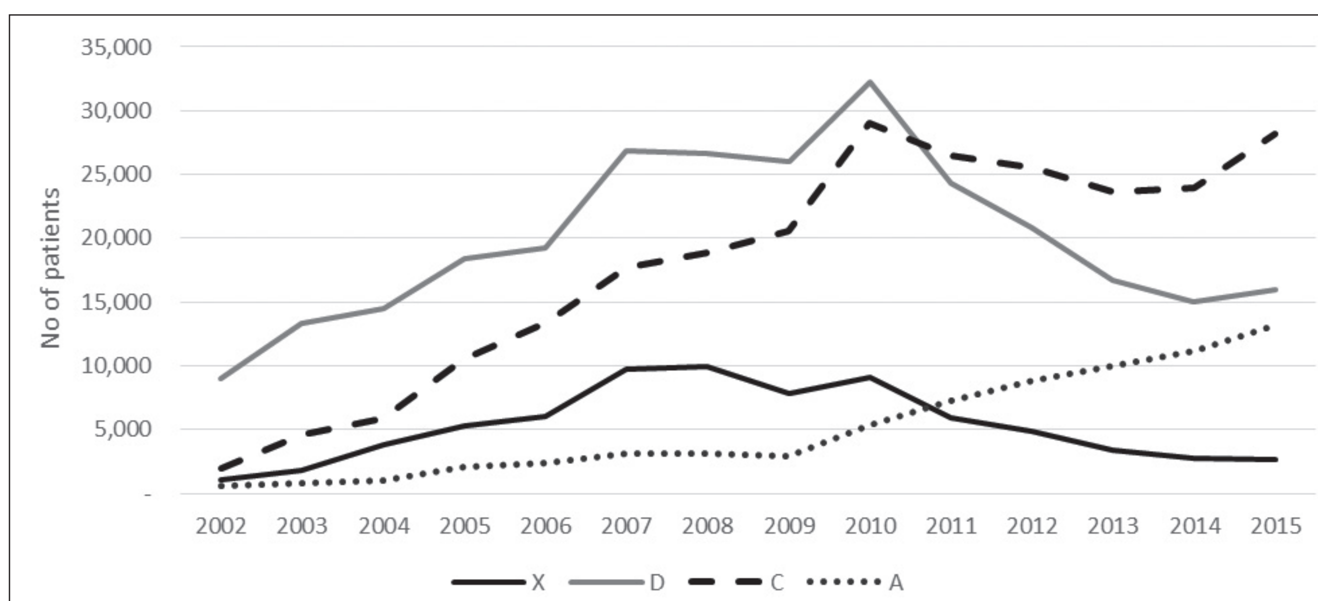


Fig. 4: Absolute number of patients with statin - macrolide co-prescriptions divided by clinical significance level

In our study, on average 253 patients on simvastatin therapy per year were co-prescribed erythromycin, which is 0.2% of patients on simvastatin therapy. Out of 597 reports in the 10-year period from 1995 to 2004, Adverse Drug Reactions Advisory Committee received 31 reports on a suspected DDI involving erythromycin. The most commonly reported interacting drugs were warfarin, statins, cisapride, anticonvulsants and ergot derivatives. This study came across nine cases of rhabdomyolysis, all with simvastatin (Australian Adverse Drug reaction Bulletin, 2006). Several case reports describe rhabdomyolysis associated with simvastatin when used in combination with erythromycin (Campbell et al. 2007; Molden and Andersson 2007; Fallah et al. 2013).

The potential consequences of DDIs are highlighted by the 50-fold increase in lovastatin induced myopathy (0.1% to 5%) when combined with erythromycin (Williams and Feely 2002; Bellosta et al. 2004; Saito and Hirata-Koizumi, 2005; Azmi et al. 2015). In our study, on average 7 patients on lovastatin therapy per year were co-prescribed erythromycin, which is 0.3% of patients on lovastatin therapy.

According to Lexi-Interact, if therapy with atorvastatin and erythromycin is necessary, the patient must be more closely monitored and the dose of atorvastatin should be as low as possible. In our study, on average 211 patients on atorvastatin therapy per year were co-prescribed erythromycin, out of which 2 were on high atorvastatin doses.

In contrast to other statin drugs, pravastatin is excreted by the renal mechanism and does not undergo significant metabolism *via* the cytochrome P450 system. According to the manufacturer, in interaction study the administration of erythromycin 500mg 3x per day with pravastatin 40mg 1x per day resulted in a statisti-

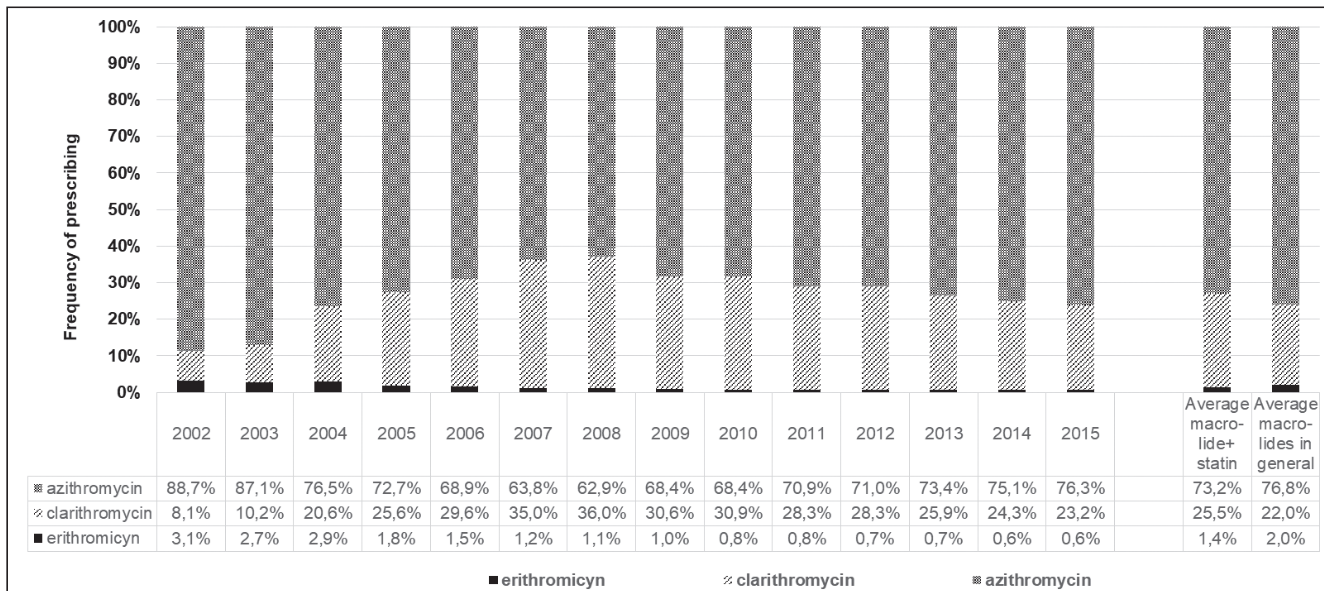


Fig. 5: Frequency of prescribing different macrolide antibiotics with statins

cally significant increase in the C_{max} (121%) and AUC (70%) of pravastatin. Therefore, the manufacturer recommends caution when pravastatin is co-administered with erythromycin or clarithromycin (Pravafenix 40mg SmPC). In our study, pravastatin is co-prescribed with different macrolides in about 0.3% of the cases (Fig. 2).

Some studies have shown an increased risk of clarithromycin-statin DDIs, especially with simvastatin (Lee and Maddix 2001; Kahri et al. 2004; Wagner et al. 2009; Hill et al. 2015; Mesgarpour et al. 2015; Hougaard et al. 2020). In our study, clarithromycin was co-prescribed with different statins, on average 25.5% of statin-macrolide co-prescriptions, and 43% of those cases were with contraindicated simvastatin, on average 5,045 cases per year. Atorvastatin is co-prescribed with clarithromycin, on average 6,375 cases per year. Lexi-Interact advises that if concomitant therapy is required, the maximum dose of atorvastatin should not exceed 20 mg. In our study, a high atorvastatin dose (60 – 80 mg) was co-prescribed with clarithromycin on average in 63 cases per year.

The study by Strandell et al. (2009) shows that rhabdomyolysis occurred shortly after initiation of azithromycin in 23% of the cases. They examined all the reports including rhabdomyolysis caused by azithromycin and statins in VigiBase (World Health Organization Adverse Drug Reactions database) to assess if the data were suggestive of an interaction. Fluvastatin was the only individual statin never co-reported to VigiBase with azithromycin and rhabdomyolysis. Case reports also indicate that there is an increased risk of rhabdomyolysis in patients taking statins concurrently with azithromycin (Grunden and Fisher 1997; Skrabal et al. 2003; Alreja et al. 2012). In our study azithromycin is co-prescribed with different statins on average in 34,321 cases per year, which is 73.2% of all cases in our study.

The risk of DDIs increases with the statin dose. The problem of potentially adverse events due to side effects from toxicity and DDIs is heightened from more widespread use of statins at increased dosages. In 2019, according to European Society of Cardiology / European Atherosclerosis Society Guidelines the treatment goal for high-risk patients is LDL-cholesterol concentra-

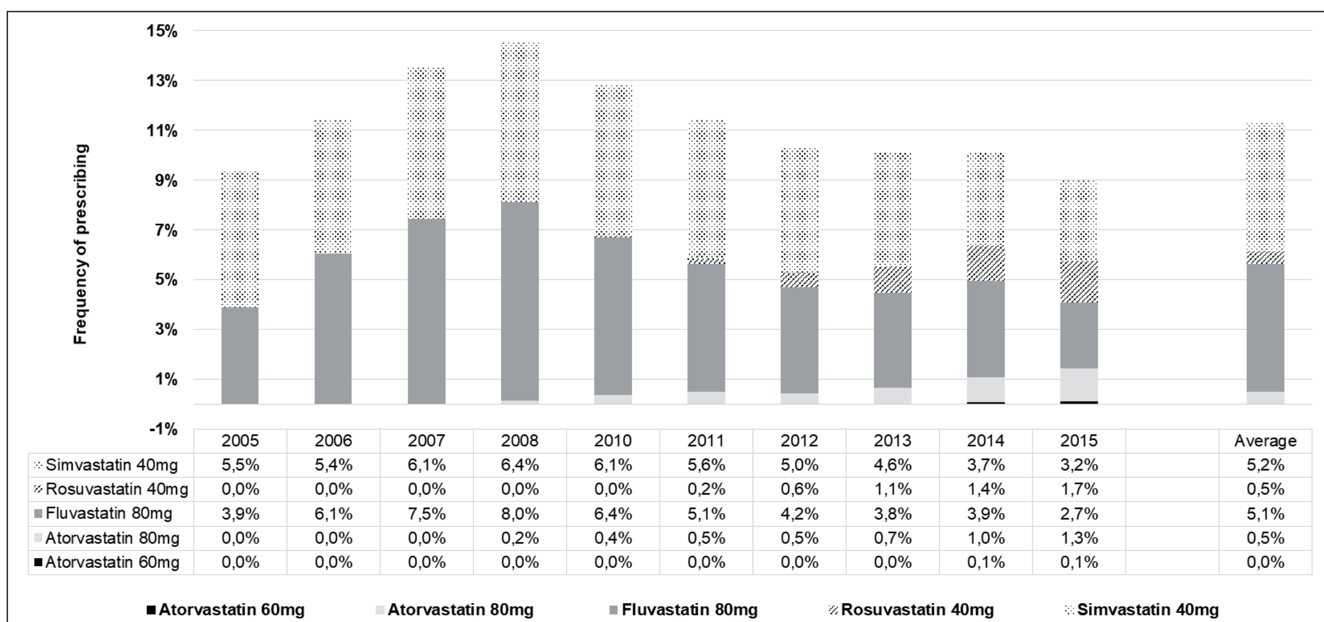


Fig. 6: Frequency of prescribing high statin dose

tion of <1.8mmol/L (<70mg/dl), which requires the use of higher statin dose. In our study, it was shown that an average of 11.5% of statin-macrolide co-prescriptions were with high-dose statins. 46% of these co-prescriptions were with simvastatin 40 mg and 4.3% with atorvastatin 60 – 80 mg (Fig. 6).

This study shows that a significantly larger number of women, rather than men, have had statin-macrolide co-prescriptions in the period studied, and that they present a significant majority in all studied groups, more than 60% of the patients (Table 5).

Table 5: Sex structure of patients receiving statin-macrolide co-prescriptions in the period 2002-2015

Statin	Macrolide	Percentage	
		Male	Female
Simvastatin	Erythromycin	37.1%	62.9%
	Clarithromycin	37.0%	63.0%
	Azithromycin	37.5%	62.5%
Lovastatin	Erythromycin	41.0%	59.0%
	Clarithromycin	38.9%	61.1%
	Azithromycin	31.1%	68.9%
Pravastatin	Erythromycin	41.9%	58.1%
	Clarithromycin	41.9%	58.1%
	Azithromycin	41.7%	58.3%
Fluvastatin	Erythromycin	47.1%	52.9%
	Clarithromycin	44.6%	55.5%
	Azithromycin	44.9%	55.1%
Atorvastatin	Erythromycin	37.6%	62.4%
	Clarithromycin	39.6%	60.4%
	Azithromycin	40.8%	59.2%
Rosuvastatin	Erythromycin	40.0%	60.1%
	Clarithromycin	39.1%	60.9%
	Azithromycin	41.4%	58.6%
Average		**39.5%**	**60.5%**

This is in accordance with the fact that the ratio of women to men on statin therapy were 1.4 in a previous study (Grgurevic et al. 2020).

Earlier studies showed that, in spite of a great increase of statin consumption in the Republic of Croatia, the local consumption is still lower than in other EU countries and that a further increase of the consumption can be expected due to the public health requirements. In that perspective, the problem of statin-macrolide co-prescription can be expected to get worse.

The evident association between the use of macrolide antibiotics combined with statins with rhabdomyolysis is very important. As the use of statins continues to rise, the chance of its concomitant use with macrolide antibiotics, which are frequently prescribed for respiratory tract and skin infections, will certainly increase.

In this study population, 15.3% of the patients on statin therapy were taking macrolide antibiotics concomitantly. On average, 90% of these co-prescriptions can lead to potentially clinically significant DDIs (X, D, C). On average, 11.5% of patients on concomitant statin-macrolide therapy were taking high-dose statins. 60% of the patients with statin-macrolide co-prescription were female. Most frequent statin-macrolide co-prescriptions were between atorvastatin and simvastatin with macrolides. As the co-prescription of statins and macrolide antibiotics in the Republic of Croatia is increasing, a rise in DDIs is expected.

3. Experimental

In Croatia, statin drugs and macrolides are issued exclusively on prescription. This study included all outpatients who were dispensed statins and macrolides through pharmacies. The research analysed retrospectively the prescribed therapy of all patients treated simultaneously with statin and macrolide antibiotics in the period of 14 years. The studied statins were: simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin and rosuvastatin. The high-dose statins studied were: simvastatin 40mg, atorvastatin 60mg, 80mg, fluvastatin 80 mg and rosuvastatin 40 mg. Macrolides included in the study were: erythromycin, clarithromycin and azithromycin.

Potential DDIs were identified by software Lexi-Comp® Lexi-Interact™ Online (Lexi-Comp, Inc., Hudson, USA), and categorized according to clinical significance into the following groups: A) No Known Interaction, B) No Action Needed, C) Monitor Therapy, D) Consider Therapy Modification, X) Avoid Combination. Interactions of level C, D and X were considered clinically significant. Studied statin-macrolide pairs are shown in Table 1.

The Croatian Health Insurance Fund (CHIF) provided data on the number of all patients to which the studied drugs were dispensed through pharmacies in the period from 2002 to 2015. The same database provided the number of patients to which macrolide was dispensed within 30 days of having been dispensed a statin. The data on statin-macrolide co-prescriptions were statistically analysed for each statin/macrolide/sex combination.

Conflicts of interest: None declared.

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