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Article

Risk factors for potential drug-drug interactions of statins in patients with acute coronary syndrome

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The aim of our study was to assess risk factors for potential drug-drug interactions (pDDIs) of statins across different phases of treatment of acute coronary syndrome (ACS) patients: from the point of first medical contact to the coronary angiography (first phase), after coronary angiography to the last day of hospitalization (second phase) and at discharge from hospital (third phase). This was a post hoc analysis of the data collected during the retrospective observational cohort study conducted at the Clinic for Cardiology of the Clinical Centre Kragujevac, Serbia. Patients prescribed statins were identified from the original study population: 156, 240 and 236 patients for the first, second and third phases, respectively. At least one statin pDDI was present in 113 (72.4%), 161 (67.1%) and 139 (58.9%) patients in the first, second and third phases, respectively. Heart failure, arrhythmias after ACS, CRP, triglycerides, length of hospitalization, number of prescribed drugs, antiarrhythmic drugs, and clopidogrel seem to increase the risk of statin pDDIs in at least one treatment phase. Physicians should be vigilant to the possibility of statin pDDIs in ACS patients who have factors that may increase their rate.

Keywords: Statins. Acute coronary syndrome. Drug-drug interactions. Risk factors.

INTRODUCTION

Statins or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors are a class of lipid-lowering drugs (Causevic-Ramosevac, Semiz, 2013). Early start of statin treatment has become a guideline-directed standard of care after acute coronary syndrome (ACS) which consists of a broad spectrum of manifestations including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (Nordmann *et al.*, 2016). Current guidelines recommend starting high-intensity statin therapy as early as possible unless contraindicated and maintaining the therapy long-term (Roffi *et al.*, 2016; Ibanez *et al.*, 2018). However, statins have a high potential for drug-drug interactions (DDIs), which may put ACS patients at high risk of adverse events such as hepatotoxicity, myopathy and rhabdomyolysis (Causevic-Ramosevac, Semiz, 2013; Kellick *et al.*, 2014; Bellosta, Corsini, 2018). DDI is defined as a clinically significant change in the exposure and/or response to a drug caused by co-administration of another drug which may lead to precipitation of an adverse event or alteration of its therapeutic effects (Scheife *et al.*, 2015). Potential DDI (pDDI) refers to a co-prescription or co-administration of two drugs known to interact (Scheife *et al.*, 2015).

Depending on the study design, population and setting from 4.6% to 36.6% of statin-treated patients may be exposed to statin pDDIs (Egger *et al.*, 2007; Rätz Bravo *et al.*, 2005; Gavronski *et al.*, 2015; Samardzic, Benkovic, Vrca, 2017; Morival *et al.*, 2018). Up to now, only a handful of studies assessed risk factors for statin pDDIs mostly in outpatients (Egger *et al.*, 2007; Rätz Bravo *et al.*, 2005; Gavronski *et al.*, 2015). In a study conducted in Switzerland, risk factors for statin pDDIs in ambulatory statin-treated dyslipidaemic patients were

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number of drugs, cardiac failure, arrhythmias and being a patient from the French-speaking part of Switzerland (Rätz Bravo *et al.*, 2005), while analysis of the data from this study according to different age groups have shown that male sex, number of pharmaceutical preparations prescribed and psychiatric disorders were risk factors in patients ≤54 years, whereas in ≥55-year-old patients risk factors were number of pharmaceutical preparations or pharmacologically active substances prescribed and a diagnosis of arrhythmia or heart failure (Egger *et al.*, 2007). In an Estonian nationwide register-based study there was a positive correlation between pDDIs and the number of concomitant medicines and age, while logistic regression analysis showed higher odds of exposure in 61–70 age group, men and simvastatin users (Gavronski *et al.*, 2015).

To the best of our knowledge, statin pDDIs and risk factors for their occurrence have not yet been evaluated in ACS patients. Therefore, the aim of our study was to assess statin pDDIs and risk factors for statin pDDIs across different phases of treatment of ACS patients.

MATERIAL AND METHODS

This was a post hoc analysis of the data collected during the retrospective observational cohort clinical study conducted at the Clinic for Cardiology of the Clinical Centre Kragujevac, a public tertiary care hospital in Kragujevac, Serbia with the aim to evaluate pDDIs across different phases of treatment of ACS patients: from the point of first medical contact to the coronary angiography (first phase), after coronary angiography to the last day of hospitalization (second phase) and at discharge from hospital (third phase) (Pejčić, Janković, Davidović, 2019). Evaluation of pDDIs across different phases of treatment was performed because of the differences in therapy before and after coronary angiography, as well as in the therapy at discharge (Pejčić, Janković, Davidović, 2019). The study is described in detail elsewhere and the Ethics Committee of the Clinical Centre Kragujevac had approved the study before its initiation (Pejčić, Janković, Davidović, 2019). Briefly, pharmacotherapy data regarding every day of the patients' treatment were collected along with demographic and clinical data (e.g. laboratory parameters at baseline, risk factors for coronary heart disease, comorbidities, Charlson comorbidity index, complications during hospitalization, reperfusion therapy) for all consecutive patients admitted to the Clinic for Cardiology between January 01, 2017 to December 31, 2017 who were older than 18 years, had diagnosis of ACS manifested as unstable angina pectoris or acute myocardial infarction with or without ST-segment elevation, who underwent coronary angiography and received at least two drugs during hospitalization longer than 24 hours (Pejčić, Janković, Davidović, 2019). Charlson *et al*. (1987) comorbidity index (CCI) is one of the most widely used indexes of comorbidity and it consists of 19 selected conditions that are weighted and summed to an index. The original study population consisted of 245 patients in which screening for pDDIs was performed in each of the previously mentioned phases of the treatment based on the drugs prescribed to them in that phase. For this post hoc analysis, we identified patients who were prescribed statin therapy: 156, 240 and 236 patients for the first, second and third phases, respectively.

Potential DDI was defined in accordance with the Consensus Recommendations for Systematic Evaluation of Drug-Drug Interaction Evidence for Clinical Decision Support as "co-prescription or co-administration of two drugs known to interact" (Scheife *et al.*, 2015). The presence of statin pDDIs was determined by Micromedex® interaction checker (available at: http://www.micromedexsolutions.com/home/dispatch). Micromedex® classifies pDDIs as Contraindicated, Major, Moderate and Minor. Potential DDIs classified as Contraindicated (the drugs are contraindicated for concurrent use), Major (the interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects) and Moderate (the interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy) were included in the analysis. Potential DDIs classified as Minor were not included in the analysis, considering that they would have limited clinical effects and generally would not require a major alteration in therapy.

All analyses were performed using the Statistical Program for Social Sciences (SPSS version 18). The data were analysed by descriptive statistics. Measures of central tendency (mean) and measures of dispersion (standard deviation and range) were used for continuous variables. Categorical variables were presented as frequencies (%). The influence of potential risk factors on the number of statin pDDIs per patient during each treatment phase was evaluated by multiple linear regression using backward elimination with a probability of F to remove a predictor of ≤ 0.1. In this approach all potential predictor variables are added into the model, then are eliminated one by one, with the variable that has the largest probability of F (i.e., *p* value) removed until all variables have a *p* value equal to or less than 0.1. Dichotomous categorical variables were coded with 0 and 1 (0 indicated the absence of a qualitative attribute, while 1 indicated presence, except for gender where 0 indicated female gender, and 1 male gender). The statistical validity of the regression was checked by analysis of variance (F value) and percentage of the outcome (number of pDDIs per patient) variability explained (R^2). The influence of potential risk factors on the outcome was assessed by their B coefficients in the regression equation, including 95% confidence intervals (CIs). A p value < 0.05 was considered statistically significant.

RESULTS

Characteristics of the study population of ACS patients who received statin therapy are shown in Table I, while pharmacotherapy and reperfusion data are shown in Table II. All patients received contrast media during coronarography in the first treatment phase. The most frequently used statin in all treatment phases was atorvastatin (see Table II for frequencies).

At least one statin pDDI was present in 113 (72.4%), 161 (67.1%) and 139 (58.9%) patients in the first, second and third phases, respectively. Average number ± standard deviation of statin pDDIs per patient in the first, second and third phases was 0.85 ± 0.63 (range: 0–3), 0.77 ± 0.63 (range: 0–3) and 0.62 ± 0.55 (range: 0–2), respectively. A total of 8 different drug pairs were involved in statin pDDIs across all treatment phases (Table III). The majority of them were pharmacokinetic (5 drug pairs, i.e. 62.5%), followed by pDDIs of unknown mechanism (2, i.e. 25.0%) and pharmacodynamic pDDIs (1, i.e. 12.5%). There were no Contraindicated pDDIs involving statins. The most frequent statin pDDI across all phases of treatment was a combination of atorvastatin and clopidogrel which may lead to decreased formation of clopidogrel active metabolite and possible high on-treatment platelet reactivity (Table III).

Results of the last step of the backward multiple linear regression analysis are shown in Table IV. Positive predictors of number of statin pDDIs, i.e. factors which may increase their rate were: heart failure (first phase), arrhythmias after ACS (second phase), CRP (first phase), triglycerides (second and third phase), length of hospitalization (second phase), number of prescribed drugs (first phase), antiarrhythmic drugs (all phases), and clopidogrel (all phases).

TABLE I - Characteristics of the study population of acute coronary syndrome patients receiving statin therapy

Variable	Mean ± standard deviation (range) or number (%)		
	First phase (*n*=156)	**Second phase (*n*=240)**	**Third phase (*n*=236)**
Age (years)	62.1 ± 9.6 (35–90)	62.2 ± 9.8 (35–90)	62.3 ± 9.8 (35–90)
Gender (male/female)	109 (69.9%)/47 (30.1%)	167 (69.6%)/73 (30.4%)	164 (69.5%)/72 (30.5%)
STEMI	74 (47.4%)	139 (57.9%)	137 (58.1%)
NSTEMI	51 (32.7%)	65 (27.1%)	62 (26.3%)

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TABLE I - Characteristics of the study population of acute coronary syndrome patients receiving statin therapy

Variable	Mean ± standard deviation (range) or number (%)		
	First phase (*n*=156)	Second phase (*n*=240)	Third phase (*n*=236)
Unstable angina pectoris	31 (19.9%)	36 (15.0%)	37 (15.7%)
Coronarography within the first 24 hours of hospitalization	90 (57.7%)	169 (70.4%)	165 (69.9%)
Length of hospitalization (days)	8.2 ± 4.2 (2–25)	8.1 ± 3.9 (2–25)	8.1 ± 3.9 (2–25)
TIMI risk score at admission	2.7 ± 1.4 (0–8)	2.7 ± 1.4 (0–8)	2.7 ± 1.5 (0–8)
Laboratory test results (first measured values)			
CK (U/L)	336.8 ± 573.7 (7–3836)	359.3 ± 635.3 (7–4204)	365.2 ± 640.6 (7–4204)
CK-MB (U/L)	35.0 ± 53.6 (6–394)	39.8 ± 66.5 (6–451)	40.4 ± 67.0 (6–451)
Troponin A2 (ng/mL)	3.597 ± 11.268 (0.000–81.000)	3.946 ± 12.724 (0.000–85.000)	4.027 ± 12.821 (0.000–85.000)
Total cholesterol (mmol/L)	5.75 ± 1.40 (3.00–13.80)	5.65 ± 1.36 (2.72–13.80)	5.63 ± 1.33 (2.72–13.80)
LDL (mmol/L)	3.62 ± 1.10 (1.28–9.31)	3.56 ± 1.11 (0.24–9.31)	3.57 ± 1.11 (0.24–9.31)
HDL (mmol/L)	1.10 ± 0.28 (0.51–2.07)	1.09 ± 0.28 (0.51–2.07)	1.09 ± 0.28 (0.51–2.07)
Triglycerides (mmol/L)	2.26 ± 1.86 (0.52–17.30)	2.24 ± 1.86 (0.52–17.30)	2.16 ± 1.60 (0.52–12.94)
Urea (mmol/L)	6.6 ± 2.7 (2.6–21.5)	6.6 ± 2.6 (2.6–21.5)	6.6 ± 2.6 (2.6–21.5)
Serum creatinine (μmol/L)	98.0 ± 31.9 (49–270)	97.4 ± 31.0 (49–270)	97.7 ± 31.0 (49–270)
CRP (mg/L)	13.9 ± 27.0 (0.3–150.4)	12.3 ± 24.5 (0.3–150.4)	12.5 ± 24.7 (0.3–150.4)
AST (IU/L)	50.5 ± 62.3 (12–557)	50.6 ± 64.5 (12–557)	50.9 ± 65.0 (12–557)
ALT (IU/L)	32.9 ± 33.6 (8–319)	32.6 ± 30.0 (7–319)	32.7 ± 30.2 (7–319)
Total bilirubin (μmol/L)	13.9 ± 7.8 (2.3–56.9)	13.6 ± 7.2 (2.3–56.9)	13.4 ± 7.0 (2.3–56.9)
Risk factors for coronary heart disease			
Hypertension	122 (78.2%)	191 (79.6%)	188 (79.7%)
Hyperlipidemia	122 (78.2%)	183 (76.3%)	179 (75.8%)
Smoking	55 (35.3%)	88 (36.7%)	86 (36.4%)
Diabetes	55 (35.3%)	82 (34.2%)	82 (34.7%)
Positive family history	46 (29.5%)	69 (28.8%)	69 (29.2%)
Obesity	7 (4.5%)	13 (5.4%)	13 (5.5%)
Comorbidities			
Charlson Comorbidity Index	2.2 ± 1.5 (0–7)	2.1 ± 1.4 (0–7)	2.1 ± 1.4 (0–7)
Asthma	5 (3.2%)	6 (2.5%)	6 (2.5%)

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TABLE I - Characteristics of the study population of acute coronary syndrome patients receiving statin therapy

Variable	Mean ± standard deviation (range) or number (%)		
	First phase (*n*=156)	Second phase (*n*=240)	Third phase (*n*=236)
Cerebrovascular diseases	15 (9.6%)	16 (6.7%)	15 (6.4%)
Chronic obstructive pulmonary disease	15 (9.6%)	18 (7.5%)	18 (7.6%)
Delirium	2 (1.3%)	6 (2.5%)	6 (2.5%)
Dementia	2 (1.3%)	2 (0.8%)	2 (0.8%)
Heart failure	4 (2.6%)	7 (2.9%)	7 (3.0%)
History of myocardial infarction/angina pectoris	7 (4.5%)	9 (3.8%)	9 (3.8%)
Liver cirrhosis	0 (0%)	0 (0%)	0 (0%)
Prior arrhythmias	5 (3.2%)	7 (2.9%)	6 (2.5%)
Renal failure	17 (10.9%)	27 (11.3%)	27 (11.4%)
Complications during hospitalization			
Arrhythmias after ACS	39 (25.0%)	68 (28.3%)	69 (29.2%)
Bleeding	12 (7.7%)	19 (7.9%)	19 (8.1%)
Infection	30 (19.2%)	44 (18.3%)	45 (19.1%)
Reinfarction	1 (0.6%)	1 (0.4%)	1 (0.4%)
Mechanical ventilation	1 (0.6%)	5 (2.1%)	5 (2.1%)

Abbreviations: ACS – acute coronary syndrome; STEMI - ST-segment elevation myocardial infarction; NSTEMI - non-ST-segment elevation myocardial infarction.

TABLE II - Pharmacotherapy and reperfusion therapy data

Variable	Mean ± standard deviation (range) or number (%)		
	First phase (*n*=156)	Second phase (*n*=240)	Third phase (*n*=236)
Number of prescribed drugs	11.7 ± 4.9 (4–33)	12.7 ± 5.0 (5–33)	9.4 ± 2.8 (4–21)
Number of different therapeutic subgroups prescribed (2nd level of ATC classification)	7.6 ± 2.9 (3–15)	8.7 ± 2.7 (4– 17)	7.2 ± 1.8 (3–12)
Number of physicians who prescribed drugs to single patient	2.9 ± 0.9 (1–9)	1.8 ± 1.2 (1–10)	–
Drug allergy noted in medical documentation	18 (11.5%)	32 (13.3%)	32 (13.6%)
Statin			
Atorvastatin	141 (90.4%)[a]	227 (94.6%)[a]	204 (86.4%)

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TABLE II - Pharmacotherapy and reperfusion therapy data

Variable	Mean ± standard deviation (range) or number (%)		
	First phase (*n*=156)	Second phase (*n*=240)	Third phase (*n*=236)
Rosuvastatin	17 (10.9%)[a]	32 (13.3%)[a]	31 (13.1%)
Pravastatin	–	–	1 (0.4%)
Pharmacological drug classes			
ACE inhibitors	91 (58.3%)	186 (77.5%)	180 (76.3%)
Analgesics	46 (29.5%)	67 (27.9%)	5 (2.1%)
Antiarrhythmic drugs	30 (19.2%)	42 (17.5%)	21 (8.9%)
Antibiotics	18 (11.5%)	73 (30.4%)	31 (13.1%)
Anticoagulants	153 (98.1%)	185 (77.1%)	28 (11.9%)
Anticonvulsants	5 (3.2%)	7 (2.9%)	5 (2.1%)
Antidepressants	2 (1.3%)	6 (2.5%)	5 (2.1%)
Antidiabetics	28 (17.9%)	70 (29.2%)	55 (23.3%)
Antipsychotics	1 (0.6%)	10 (4.2%)	3 (1.3%)
Beta-blockers	82 (52.6%)	181 (75.4%)	184 (78.0%)
Bronchodilators	24 (15.4%)	33 (13.8%)	20 (8.5%)
Calcium channel blockers	28 (17.9%)	53 (22.1%)	53 (22.5%)
Corticosteroids	8 (5.1%)	7 (2.9%)	7 (3.0%)
Diuretics	62 (39.7%)	123 (51.3%)	120 (50.8%)
Nitrates	94 (60.3%)	115 (47.9%)	112 (47.5%)
Proton pump inhibitors	146 (93.6%)	234 (97.5%)	218 (92.4%)
Antiplatelet therapy	156 (100.0%)	240 (100.0%)	235 (99.6%)
– Aspirin	156 (100.0%)	240 (100.0%)	234 (99.2%)
– P2Y12 inhibitor – Clopidogrel	116 (74.4%)	154 (64.2%)	140 (59.3%)
– P2Y12 inhibitor – Ticagrelor	48 (30.8%)	101 (42.1%)	86 (36.4%)
– Glycoprotein IIb/IIIa inhibitor – Eptifibatide	5 (3.2%)	3 (1.3%)	0 (0.0%)
Reperfusion therapy			
Primary PCI	117 (75.0%)	192 (80.0%)	188 (79.7%)
CABG indicated	24 (15.4%)	27 (11.3%)	27 (11.4%)
Fibrinolytic therapy followed by rescue PCI	3 (1.9%)	7 (2.9%)	7 (3.0%)
No reperfusion therapy	12 (7.7%)	14 (5.8%)	14 (5.9%)

[a] Switch from atorvastatin to rosuvastatin or vice versa occurred in 2 patients in first phase and 19 patients in second phase
Abbreviations: ATC - Anatomical Therapeutic Chemical; ACE - Angiotensin-converting enzyme; PCI - percutaneous coronary intervention; CABG - Coronary artery bypass graft.

TABLE III – Frequency and description of detected statin potential drug-drug interactions across phases of treatment

Combination	Severity	Possible clinical outcome	Phase: *n* (%)		
			First (*n*=156)	Second (*n*=240)	Third (*n*=236)
Atorvastatin + clopidogrel	Moderate	↓ formation of clopidogrel active metabolite and possible high on-treatment platelet reactivity	105 (67.3%)	143 (59.6%)	122 (51.7%)
Atorvastatin + amiodarone	Moderate	↑ risk of myopathy or rhabdomyolysis	19 (12.2%)	31 (12.9%)	16 (6.8%)
Rosuvastatin + amiodarone	Moderate	↑ serum transaminase levels	1 (0.6%)	6 (2.5%)	5 (2.1%)
Atorvastatin + azithromycin	Moderate	↑ risk of rhabdomyolysis	3 (1.9%)	3 (1.3%)	1 (0.4%)
Atorvastatin + digoxin	Major	↑ plasma concentrations of digoxin	2 (1.3%)	1 (0.4%)	0 (0.0%)
Atorvastatin + fenofibrate	Major	↑ risk of myopathy or rhabdomyolysis	0 (0.0%)	1 (0.4%)	2 (0.8%)
Atorvastatin + verapamil	Major	↑ risk of myopathy or rhabdomyolysis	2 (1.3%)	0 (0.0%)	0 (0.0%)
Atorvastatin + clarithromycin	Major	↑ risk of myopathy or rhabdomyolysis	1 (0.6%)	0 (0.0%)	0 (0.0%)

↑ – increased, ↓ – decreased.

TABLE IV - Risk factors for statin potential drug-drug interactions in acute coronary syndrome patients across phases of treatment

Variable	First phase (*n*=156)			Second phase (*n*=240)			Third phase (*n*=236)		
	B	95%CI	*p*	B	95%CI	*p*	B	95%CI	*p*
Constant	–	–	–	–0.213	–0.343; –0.084	0.001*	–0.268	–0.522; –0.015	0.038*
Heart failure	0.485	0.107; 0.863	0.012*	–	–	–	–	–	–
Arrhythmias after ACS	–	–	–	0.166	0.063; 0.270	0.002*	–	–	–
CRP	0.003	0.000; 0.005	0.026*	–	–	–	–	–	–
Triglycerides	–	–	–	0.032	0.009; 0.055	0.007*	0.041	0.018; 0.064	0.001*
Length of hospitalization	–	–	–	0.021	0.010; 0.032	0.000*	–	–	–

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TABLE IV - Risk factors for statin potential drug-drug interactions in acute coronary syndrome patients across phases of treatment

Variable	First phase (*n*=156)			Second phase (*n*=240)			Third phase (*n*=236)		
	B	95%CI	*p*	B	95%CI	*p*	B	95%CI	*p*
Number of prescribed drugs	0.018	0.005; 0.032	0.008*	–	–	–	–	–	–
Antiarrhythmic drugs	0.675	0.526; 0.824	0.000*	0.726	0.600; 0.851	0.000*	0.894	0.769; 1.019	0.000*
Clopidogrel	0.833	0.698; 0.968	0.000*	0.890	0.802; 0.979	0.000*	0.832	0.758; 0.906	0.000*
R^2; F (*p*)	0.683; 53.519 (0.000*)			0.726; 124.012 (0.000*)			0.747; 170.474 (0.000*)		

Abbreviations: ACS – acute coronary syndrome; CRP – C-reactive protein; B – Unstandardized coefficient; CI – Confidence interval; p – Statistical significance; * Statistically significant ($p < 0.05$).

List of variables entered at the beginning of the analysis (variables included in the last step of the model are marked with †):

First phase: age, gender†, Charlson Comorbidity Index, heart failure†, renal failure, hyperlipidaemia, diabetes, CRP†, triglycerides, number of physicians who prescribed drugs to single patient, number of prescribed drugs†, antiarrhythmic drugs†, clopidogrel†, antibiotics, calcium channel blockers;

Second phase: age, gender, length of hospitalization†, Charlson Comorbidity Index, dementia, infection during hospitalization, heart failure, arrhythmias after ACS†, asthma, renal failure, hyperlipidaemia, diabetes, triglycerides†, number of physicians who prescribed drugs to single patient, number of prescribed drugs, antiarrhythmic drugs†, antibiotics, clopidogrel†;

Third phase: age†, gender, length of hospitalization, Charlson Comorbidity Index, dementia, arrhythmias after ACS, asthma, heart failure, renal failure, hyperlipidaemia, diabetes, triglycerides†, number of prescribed drugs, antiarrhythmic drugs†, antibiotics, clopidogrel†.

DISCUSSION

The majority of ACS patients (over 58.9%) in our study were exposed to at least one statin pDDI across all treatment phases. In at least one phase heart failure, arrhythmias after ACS, CRP, triglycerides, length of hospitalization, number of prescribed drugs, antiarrhythmic drugs and clopidogrel seem to increase the risk of pDDIs in ACS patients.

Percentage of patients exposed to statin pDDIs in previous studies ranged from 4.6% in Estonian nationwide study in subjects aged 50 years or older (Gavronski *et al*., 2015) to 36.6% in subjects in Croatian community pharmacy (Samardzic, Benkovic, Vrca, 2017) which is lower than the percentage in our study probably due to differences in study populations, settings, considered types of pDDIs and information sources used to define pDDIs. Our study was conducted in ACS patients hospitalized in a tertiary care hospital which usually have more severe clinical conditions, so prevalence and pattern of pDDIs observed in our study may differ from ambulatory patients or patients hospitalized in other settings (Morival *et al*., 2018).

The number of prescribed drugs significantly increased the risk of statin pDDIs in line with previous studies (Egger *et al*., 2007; Rätz Bravo *et al*., 2005; Gavronski *et al*., 2015). ACS patients who are prescribed a higher number of drugs in general have a higher risk to be exposed to pDDIs (Pejčić, Janković, Davidović, 2019). In addition, length of hospitalization was observed to be a significant risk factor for statin pDDIs in our study, as well as for pDDIs in general in ACS (de Lima, de Godoy, 2017) and cardiovascular patients (Kovačević

et al., 2017). It seems that longer hospitalization may increase the risk of getting a drug that may interact with statins, particularly in the second phase of treatment.

Increased triglyceride levels were associated with the increased number of statin pDDIs in our study. Considering that statin-fibrate combination therapy may have to be used to treat patients with ACS complicated by elevated triglycerides (Li *et al*., 2013), this combination therapy probably contributed to this finding. Combined statin and fibrate therapy may lead to rhabdomyolysis and according to the recommendations of the American Heart Association fenofibrate is the preferred fibrate to use in combination with statins because of a reduced incidence of DDIs compared with statin-gemfibrozil combination therapy (Wiggins *et al.*, 2016). However, even a combination with fenofibrate was associated with the occurrence of rhabdomyolysis in ACS patients, so caution is certainly needed even when fenofibrate is prescribed (Jozic *et al*., 2014). CRP, a prognostic marker of recurrent nonfatal myocardial infarction or cardiac death in NSTEMI, and marker which may reflect the extent of myocardial injury in STEMI (del Val Martin, Sanmartín Fernández, Zamorano Gómez, 2015), was also associated with increased risk of statin pDDIs in our study.

Arrhythmias and heart failure increased the risk of statin pDDIs in our study. This finding is in line with previous studies conducted in ambulatory statin-treated dyslipidaemic patients (Egger *et al.*, 2007; Rätz Bravo *et al.*, 2005). These diagnoses may act as surrogate markers for use of drugs known to interact with statins: digoxin and antiarrhythmic drugs, especially amiodarone (Egger *et al.*, 2007; Rätz Bravo *et al.*, 2005). Certain statins (e.g. simvastatin, lovastatin and atorvastatin) may increase the plasma digoxin concentration due to inhibition of P-glycoprotein, which can be concerning considering its narrow therapeutic range (Rätz Bravo *et al.*, 2005). Amiodarone is a cytochrome P450 (CYP) 3A4 and CYP2C9 inhibitor which may increase levels of statins metabolized via these enzymes and risk of adverse effects (Egger *et al.*, 2007).

Clopidogrel is a prodrug that requires conversion via the CYP system (dominantly by CYP3A4, CYP3A5 and CYP2C19) (Todorović *et al.*, 2016; Thotakura *et al.*, 2018). Drugs interfering with or being co-metabolized via those enzymes, like statins metabolized via CYP3A4, might decrease its antiplatelet effect and increase the risk of thrombotic events (Todorović *et al.*, 2016; Thotakura *et al.*, 2018). Lau *et al.* (2003) first reported results of an ex vivo study showing that atorvastatin, but not pravastatin, attenuated clopidogrel antiplatelet effects in a dose-dependent manner. In the following years, many conflicting reports regarding this pDDI were published (Steinhubl, Akers, 2006). Although some studies reported that CYP3A4 metabolized statins decrease clopidogrel antiplatelet effects, the majority of them, however, found no influence of statin therapy on platelet function which highlighted the limitations in translating ex vivo platelet testing results to clinical practice and cardiovascular outcomes (Steinhubl, Akers, 2006). The majority of studies involving ACS patients didn't show reduced clinical efficacy of clopidogrel when it was used concomitantly with statins (Ojeifo *et al.*, 2013; Mukherjee *et al.*, 2005). However, some studies suggest that patients with high on-treatment platelet reactivity (HPR) during concurrent use of clopidogrel and atorvastatin may benefit from switching to a non-CYP3A4-metabolized statin which can significantly decrease platelet reactivity and the prevalence of HPR (Park *et al.*, 2012). Also, hepatotoxicity may occur when clopidogrel is used concomitantly with atorvastatin probably due to increased stress on the CYP3A4 enzyme (Thotakura *et al.*, 2018).

When initiating therapy with a statin, both the existing treatment regimen and the risk profile of the patient should be carefully evaluated. The overall clinical impact of a DDI can range from mild to life-threatening, so not all DDIs require a modification in therapy (Wiggins *et al.*, 2016). The variability of the clinical significance of a DDI depends on medication-specific and patient-specific factors, so it is important to evaluate the risk-benefit ratio of the combination therapy individually for each patient (Wiggins *et al.*, 2016).

Our work has some limitations that need to be considered. First, the study was unicentric, which could have introduced bias of local and national quality of medical education in the results. In addition, the study was retrospective, so we could only analyse potential statin DDIs, while their clinical outcomes could

not be followed. Although the use of an interaction checker is helpful in identifying pDDIs, this also has its limitations: it is not possible to control for factors influencing the relevance of a pDDI (e.g. dosage, time of administration, beginning and duration of treatment, underlying diseases) (Egger *et al.*, 2007). Actual DDIs, i.e. actual clinical manifestations of pDDIs can be difficult to identify. Some adverse events associated with statin pDDIs e.g. musculoskeletal adverse events occur rarely or may have delayed onset ranging from occurring within 12 months or many years after starting statin therapy (Akimoto *et al.*, 2018) and many factors (such as concomitant disease or genetic predisposition) could make the causality assessment of the interaction difficult (Magro, Moretti, Leone, 2012). Despite these limitations, our findings may serve as a useful input to understand the extent of the problem and taking measures to improve the management of statin DDIs in ACS patients.

In conclusion, the majority of ACS patients in our study were exposed to at least one statin pDDI across all treatment phases. Heart failure, arrhythmias after ACS, CRP, triglycerides, length of hospitalization, number of prescribed drugs, antiarrhythmic drugs, and clopidogrel seem to increase the risk of statin pDDIs in ACS patients. Physicians should be vigilant to the possibility of statin pDDIs in patients who have factors that may increase their rate.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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