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Drug–drug interactions in patients with acute coronary syndrome across phases of treatment

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Abstract

The objective of this study is to evaluate potential drug–drug interactions (pDDIs) and risk factors for pDDIs in three phases of an acute coronary syndrome (ACS) treatment: 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 retrospective observational cohort clinical study was conducted at the Clinic for Cardiology of the Clinical Centre Kragujevac, a public tertiary care hospital in Kragujevac, Serbia. Micromedex® interaction checker was used to detect pDDIs. This study included 245 ACS patients. All patients were exposed to at least one pDDI in all the phases of treatment. Mean total number of pDDIs was 9.47 ± 6.07, 10.11 ± 6.92, and 6.29 ± 3.66 in first, second, and third phases, respectively. Age, > 6 h from the beginning of the symptoms to admission, primary PCI, STE-ACS, COPD, delirium, hyperlipidemia, hypertension, obesity, systolic blood pressure at admission, TIMI risk score at admission, ALT, LDL, number of physicians who prescribed drugs to a single patient, number of prescribed drugs, and various pharmacological classes increased risk of pDDIs. Mechanical ventilation, dementia, and drug allergy noted in the medical documentation protected against them. Effects of heart failure, diabetes, and aPTT depended on phase of treatment and severity of pDDI. In conclusion, physicians should be vigilant to the possibility of pDDIs in patients harbouring factors that may increase their rate.

Keywords Acute coronary syndrome · Drug–drug interactions · Risk factors · Phases of treatment

Introduction

Acute coronary syndrome (ACS) is an important cause of morbidity and mortality worldwide, and its clinical manifestations include ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UAP) [1]. Evaluation of coronary anatomy by coronary angiography provides crucial information needed to select the most appropriate treatment strategy in ACS patients: percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) surgery, or medical therapy [2–4]. Initial and long-term treatment of ACS involves multiple medications with some differences in their use before and after coronary angiography [2, 3, 5]. In addition, ACS patients usually have other comorbidities requiring long-term pharmacotherapy, which put them in high risk of drug–drug interactions (DDIs) [2, 3, 5].

DDI is defined as a "clinically meaningful alteration in the exposure and/or response to a drug (object drug) that has occurred as a result of the co-administration of another drug (precipitant drug)" [6]. Response may refer to either precipitation of an adverse event or alteration of the therapeutic effect of the object drug [6]. Potential DDI (pDDI) is defined as the "co-prescription or co-administration of two drugs known to interact," meaning that a DDI, i.e., its manifestation, could occur in the exposed patient [6]. The majority of the previous studies assessed pDDIs in all patients who were

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hospitalized on either cardiology wards or cardiac intensive-care units [7–14]. These studies show a high prevalence of pDDIs (up to 97%), while results regarding the influence of majority of the assessed risk factors (age, gender, number of comorbidities, and length of hospitalization) are inconsistent [7–14]. Only the number of prescribed drugs is consistently associated with the occurrence of pDDIs [7–14]. To the best of our knowledge, only one study up to now assesses pDDIs in ACS patients [15]. An analysis of 607 prescriptions from 119 hospitalized ACS patients shows that 99% of the prescriptions have at least one pDDI [15]. Correlation between the number of pDDIs and three variables is assessed in that analysis: age, days of hospitalization, and number of drugs [15]. Only the days of hospitalization and number of drugs are significantly positively correlated with the number of pDDIs [15].

The previous studies do not pay a particular attention to the different phases of treatment of ACS when evaluating pDDIs. Considering the crucial role of coronary angiography in the treatment of ACS and differences in therapy before and after it is performed, as well as in the therapy at discharge, the main objective of this study is to evaluate pDDIs and risk factors for individual severity categories of pDDIs across different phases of treatment of ACS patients.

Methods

This retrospective observational cohort clinical study was conducted at the Clinic for Cardiology of the Clinical Centre Kragujevac, a public tertiary care hospital in Kragujevac, Serbia. The Ethics Committee of the Clinical Centre Kragujevac had approved the study prior to its initiation.

The cohort consisted of all consecutive patients admitted to the Clinic for Cardiology between January 01, 2017 and December 31, 2017 who were older than 18 years, had a diagnosis of ACS manifested as unstable angina pectoris (ICD-10: I20.0) or acute myocardial infarction with or without ST-segment elevation (ICD-10: I21, I22), who underwent coronary angiography, and received at least two drugs during a hospitalization longer than 24 h. Exclusion criteria were: pregnancy, incomplete medical documentation, pre-existing innate or acquired disorders of haemostasis, and administration of drugs affecting haemostasis prior to the moment that patient was considered eligible for inclusion in the study.

The data were collected from the patients' medical records. Pharmacotherapy data regarding every day of the patients' treatment were collected. All drugs were classified in accordance with Anatomical Therapeutic Chemical (ATC) Classification [16]. The following variables were taken into account: age, gender, length of hospitalization, manifestation of ACS (STEMI [STE-ACS]; NSTEMI, UAP [NSTE-ACS]), time elapsed from the beginning of the symptoms to admission (< 2 h, 2–6 h, 6–12 h, 12–24 h, > 24 h), arrival by ambulance, timing of coronary angiography (within 24 h of hospitalization or later), the Thrombolysis in Myocardial Infarction (TIMI) risk score at admission, heart rate (at admission, in second and third phases), systolic and diastolic blood pressure (at admission, in second and third phases), corrected QT (QTc) interval according to Bazett's formula (at admission, in second and third phases), laboratory parameters at baseline [first measured values of creatine kinase (CK), creatine kinase—MB (CK-MB), troponin A2, urea, serum creatinine, white and red blood cell count, platelet count, hemoglobin, potassium, international normalized ratio (INR), activated partial thromboplastin time (aPTT), blood glucose level, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, C-reactive protein (CRP), total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides], risk factors for coronary heart disease (diabetes, hypertension, hyperlipidemia, smoking, obesity, and positive family history), comorbidities [especially presence of dementia, delirium, heart failure, renal failure, liver cirrhosis, chronic obstructive pulmonary disease (COPD), asthma, prior arrhythmias, cerebrovascular diseases, history of myocardial infarction/angina pectoris, and anemia], Charlson Comorbidity Index (CCI), complications during hospitalization [reinfarction, bleeding, arrhythmias after ACS, infections—e.g., urinary tract infection (UTI), pneumonia, *Clostridium difficile* infection, and others], mechanical ventilation, type of reperfusion therapy (PCI, CABG surgery, fibrinolytic therapy, and no reperfusion therapy), angiographic information (number of diseased vessels, lesion location, i.e., diseased coronary artery or arteries, and number of implanted stents), pharmacotherapy data regarding all drugs prescribed to each patient [number of prescribed drugs, number of different therapeutic subgroups prescribed (second level of ATC classification), prescribing antiarrhythmic drugs, antibiotics, antidiabetics, antidepressants, analgesics, anticoagulants, anticonvulsants, antipsychotics, corticosteroids, statins, ACE inhibitors, beta-blockers, calcium channel blockers, bronchodilators, proton-pump inhibitors, contrast media, antiplatelet therapy, diuretics or nitrates, drug allergy noted in the medical documentation, and number of physicians who prescribed drugs to a single patient], and interaction checker data (number and description of the pDDI).

A 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" [6]. The presence and classification of pDDIs was determined by Micromedex® interaction checker, which classifies pDDIs as Contraindicated, Major, Moderate, and Minor [17].

Screening for pDDIs was performed in three phases of treatment: 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).

All analyses were performed using Statistical Program for Social Sciences (SPSS version 18). The data were analyzed by descriptive statistics. Measures of central tendency (mean and median) and measures of dispersion (standard deviation and range) were used for continuous variables. Categorical variables were presented as frequencies (%).

Differences in number of pDDIs per patient across three phases of treatment were assessed by Friedman non-parametric test (Kolmogorov–Smirnov test showed non-normal distribution of these variables). In case of a significant difference, post hoc testing involved individual Wilcoxon signed-rank tests using a Bonferroni adjusted alpha value to control for type 1 error. After applying Bonferroni correction for number of comparisons (three), revised alpha level for determining statistical significance was $0.05/3 = 0.0167$.

The influence of potential risk factors on the number of different severity categories of pDDIs per patient during each phase of treatment was evaluated by hierarchical multiple linear regression analysis. The potential predictor variables were entered in the first block. A complete list of entered variables is provided in Supplementary Text 1 in Electronic Supplementary Material. Interaction terms created by multiplying two predictors were entered in the second block to test for moderator effects: NSTE-ACS × coronary angiography after 24 h of hospitalization (first phase), CCI × length of hospitalization (all phases), and Diabetes × hypertension (all phases). Continuous variables (CCI and length of hospitalization) were centred by subtracting the sample mean from the individual value before interaction terms were formed to avoid multicollinearity. 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). 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

This study includes 245 ACS patients. ACS is manifested as STEMI in 140 (57.1%) patients, while 67 (27.3%) and 38 (15.5%) patients have NSTEMI and UAP, respectively. Distribution of the patients according to the time elapsed from the first occurrence of the symptoms to the admission is as follows: 59 patients (24.1%) were admitted within the first 2 h, 61 patients (24.9%) were admitted after 2–6 h, 39 patients (15.9%) after 6–12 h, 22 patients (9.0%) after 12–24 h, and 64 patients (26.1%) after 24 h. One hundred and fourteen patients (46.5%) arrived by ambulance. Coronary angiography was performed within 24 h of hospitalization in 171 (69.8%) patients: 126 (90.0%) STEMI (STE-ACS) patients and 45 (42.9%) NSTE-ACS patients. Most patients have single-vessel disease ($n = 172$; 70.2%). Two-vessel disease is identified in 43 (17.6%) patients and three-vessel disease in 30 (12.2%) patients. The lesions are most frequently located in the left anterior descending artery ($n = 163$, i.e., 66.5% of patients), followed by the right coronary artery ($n = 115$; 46.9%), left circumflex artery ($n = 60$; 24.5%), and left main coronary artery ($n = 10$; 4.1%). The majority of patients underwent primary PCI ($n = 196$; 80.0%). CABG surgery was indicated in 28 patients (11.4%), while only 7 patients (2.9%) were treated with fibrinolytic therapy followed by rescue PCI. One stent was implanted in 138 patients (56.3%), two stents in 38 patients (15.5%), and three or more stents in 27 patients (11.0%). Reperfusion therapy was not initiated in 14 patients (5.7%). Mechanical ventilation was used in 5 patients (2.0%). Other characteristics of the study population are reported in Table 1, while Table 2 reports pharmacotherapy data. Drug allergy was noted in the medical documentation of 34 patients (13.9%).

All patients had at least one pDDI in all three phases of treatment (Table 3). There was a significant difference in the number of pDDIs among phases of treatment, both in terms of total number of pDDIs and number of individual severity categories of pDDIs. Although the total number of pDDIs is highest in second phase, a significant difference is found between first and third phases, and second and third phases, but not between first and second phases of treatment, indicating that the total number of pDDIs is lowest in third phase. Post hoc analysis in terms of number of individual severity categories of pDDIs shows some similarities: number of pDDIs is always significantly lower in third compared to second phase. However, comparisons between first and second phases and first and third phases show some differences. The number of Major pDDIs is higher in first compared to second phase, while the number of Moderate pDDIs is higher in second compared to first phase. On the other hand, the number of Contraindicated, Major, and Minor pDDIs is significantly lower in third compared to first phase.

Table 4 provides a description and frequency of Contraindicated pDDIs across the phases of treatment. The most common pDDIs of other severity categories are provided in Supplementary Table 1. An increased risk of bleeding is the most common possible clinical outcome of pDDIs in first treatment phase (Supplementary Fig. 1). Effects on cardiovascular system with possible changes in blood pressure,

Table 1 Characteristics of the study population ($n = 245$)

Variable	Mean ± standard deviation; median (range) or number (%)		
Age (years)	62.3 ± 9.7; 62.0 (35–90)		
Gender (male/female)	169 (69.0%)/76 (31.0%)		
Length of hospitalization (days)	8.1 ± 3.9; 7.0 (2–25)		
TIMI risk score at admission	2.7 ± 1.5; 3.0 (0–8)		
	At admission	In second phase	In third phase
Heart rate (beats per minute)	78.6 ± 19.2; 77.0 (32–142)	76.7 ± 15.5; 75.0 (52–144)	69.7 ± 8.6; 69.0 (53–83)
Systolic blood pressure (mmHg)	144.5 ± 28.5; 145.0 (60–220)	125.8 ± 15.9; 125 (100–195)	124.2 ± 13.2; 125 (90–175)
Diastolic blood pressure (mmHg)	84.6 ± 17.9; 85.0 (30–135)	76.6 ± 9.2; 80 (60–105)	70.3 ± 8.0; 70 (60–95)
QTc interval (ms)	421.1 ± 27.4; 409 (383–487)	424.1 ± 21.5; 419 (367–466)	435.7 ± 37.6; 424 (378–565)
Laboratory test results (first measured values)			
CK (U/L)	356.7 ± 630.6; 155.0 (7–4204)		
CK-MB (U/L)	39.8 ± 66.0; 18.0 (6–451)		
Troponin A2 (ng/mL)	3.889 ± 12.602; 0.275 (0.000–85.000)		
INR	1.06 ± 0.09; 1.05 (0.90–1.50)		
aPTT (s)	28.7 ± 11.0; 27.7 (20.2–188.8)		
Total cholesterol (mmol/L)	5.64 ± 1.36; 5.60 (2.72–13.80)		
LDL (mmol/L)	3.56 ± 1.11; 3.47 (0.24–9.31)		
HDL (mmol/L)	1.09 ± 0.27; 1.08 (0.51–2.07)		
Triglycerides (mmol/L)	2.23 ± 1.85; 1.80 (0.52–17.30)		
Urea (mmol/L)	6.6 ± 2.6; 6.1 (2.6–21.5)		
Serum creatinine (μmol/L)	97.3 ± 31.0; 91.0 (49–270)		
Red blood cell count (10^{12}/L)	4.7 ± 0.5; 4.7 (3.1–7.7)		
Hemoglobin (g/L)	140.3 ± 14.7; 142.0 (96–178)		
White blood cell count (10^9/L)	10.4 ± 3.4; 9.9 (4.9–26.6)		
CRP (mg/L)	12.2 ± 24.2; 4.5 (0.3–150.4)		
Platelet count (10^9/L)	246.2 ± 60.0; 239.0 (135–457)		
Potassium (mmol/L)	4.2 ± 0.5; 4.2 (2.9–5.9)		
Blood glucose level (mmol/L)	8.3 ± 4.0; 7.2 (3.9–29.6)		
AST (IU/L)	50.3 ± 63.9; 31.0 (12–557)		
ALT (IU/L)	32.3 ± 29.8; 25.0 (7–319)		
Total bilirubin (μmol/L)	13.6 ± 7.2; 12.2 (2.3–56.9)		
Risk factors for coronary heart disease			
Hypertension	195 (79.6%)		
Hyperlipidemia	187 (76.3%)		
Smoking	88 (35.9%)		
Diabetes	85 (34.7%)		
Positive family history	70 (28.6%)		
Obesity	14 (5.7%)		
Comorbidities			
Charlson comorbidity index (CCI)	2.1 ± 1.5; 2.0 (0–7)		
Anemia	36 (14.7%)		
Asthma	6 (2.4%)		
Cerebrovascular diseases	16 (6.5%)		
Chronic obstructive pulmonary disease (COPD)	18 (7.3%)		
Delirium	6 (2.4%)		
Dementia	2 (0.8%)		
Heart failure	7 (2.9%)		
History of myocardial infarction/angina pectoris	9 (3.7%)		

Table 1 (continued)

Variable	Mean ± standard deviation; median (range) or number (%)
Liver cirrhosis	0 (0.0%)
Prior arrhythmias	7 (2.9%)
Renal failure	28 (11.4%)
Complications during hospitalization	
Arrhythmias after ACS	70 (28.6%)
Bleeding	19 (7.8%)
Infections [UTI; pneumonia; *C. difficile* infection; other]	46 (18.8%) [9 (3.7%); 22 (9.0%); 2 (0.8%); 13 (5.3%)]
Reinfarction	1 (0.4%)

Table 2 Pharmacotherapy data

Variable	Mean ± standard deviation; median (range) or number (%)		
	First phase (*n* = 245)	Second phase (*n* = 245)	Third phase (*n* = 245)
Number of prescribed drugs	10.3 ± 4.6; 9.0 (4–33)	12.7 ± 5.0; 12.0 (4–33)	9.4 ± 2.9; 9.0 (4–21)
Number of different therapeutic subgroups prescribed (second level of ATC classification)	6.7 ± 2.9; 6.0 (2–15)	8.7 ± 2.7; 8.0 (2– 17)	7.2 ± 1.9; 7.0 (3–12)
Number of physicians who prescribed drugs to a single patient	2.9 ± 0.9; 3.0 (1–9)	1.8 ± 1.2; 1.0 (1–10)	–
Pharmacological drug classes			
ACE inhibitors	120 (49.0%)	190 (77.6%)	187 (76.3%)
Analgesics	69 (28.2%)	67 (27.3%)	5 (2.0%)
Antiarrhythmic drugs	56 (22.9%)	43 (17.6%)	22 (9.0%)
Antibiotics	20 (8.2%)	75 (30.6%)	32 (13.1%)
Anticoagulants	241 (98.4%)	187 (76.3%)	29 (11.8%)
Anticonvulsants	5 (2.0%)	7 (2.9%)	6 (2.4%)
Antidepressants	2 (0.8%)	6 (2.4%)	5 (2.0%)
Antidiabetics	35 (14.3%)	72 (29.4%)	57 (23.3%)
Antipsychotics	1 (0.4%)	10 (4.1%)	3 (1.2%)
Beta-blockers	111 (45.3%)	184 (75.1%)	187 (76.3%)
Bronchodilators	27 (11.0%)	33 (13.5%)	20 (8.2%)
Calcium channel blockers	38 (15.5%)	55 (22.4%)	57 (23.3%)
Contrast media	245 (100.0%)	0 (0.0%)	0 (0.0%)
Corticosteroids	8 (3.3%)	7 (2.9%)	7 (2.9%)
Diuretics	78 (31.8%)	127 (51.8%)	126 (51.4%)
Nitrates	135 (55.1%)	118 (48.2%)	118 (48.2%)
Proton-pump inhibitors	224 (91.4%)	238 (97.1%)	226 (92.2%)
Statins	156 (63.7%)	240 (98.0%)	236 (96.3%)
Antiplatelet therapy	245 (100.0%)	245 (100.0%)	244 (99.6%)
Aspirin	245 (100.0%)	245 (100.0%)	243 (99.2%)
P2Y12 inhibitor—clopidogrel	170 (69.4%)	156 (63.7%)	145 (59.2%)
P2Y12 inhibitor—ticagrelor	85 (34.7%)	104 (42.4%)	89 (36.3%)
Glycoprotein IIb/IIIa inhibitor—eptifibatide	10 (4.1%)	3 (1.2%)	0 (0.0%)

heart rate, or rhythm are most common in second and third phases.

The results of the hierarchical multiple linear regression analysis are shown in Table 5 and Supplementary Table 2. A consistent positive association with the number of pDDIs is found in at least one of the phases for following variables: age (third phase), > 6 h from the beginning of the symptoms to admission (first phase), primary PCI (first phase), STE-ACS (second phase), COPD (first phase), delirium (second phase), hyperlipidemia (first and third phase), hypertension

Table 3 Number of potential drug–drug interactions in ACS patients across phases of treatment

Type of interaction	Mean ± standard deviation; median (range)			Friedman test	Post hoc Wilcoxon tests		
	First phase ($n=245$)	Second phase ($n=245$)	Third phase ($n=245$)		First vs. second phase	First vs. third phase	Second vs. third phase
Contraindicated	0.21 ± 0.42; 0.00 (0–2)	0.23 ± 0.43; 0.00 (0–2)	0.01 ± 0.09; 0.00 (0–1)	χ^2 (2) = 56.516, $p=0.000$*	$Z=-0.647$, $p=0.518$	$Z=-6.607$, $p=0.000$**	$Z=-7.285$, $p=0.000$**
Major	5.25 ± 3.01; 4.00 (1–20)	4.58 ± 3.62; 3.00 (0–18)	2.62 ± 1.79; 2.00 (0–10)	χ^2 (2) = 185.556, $p=0.000$*	$Z=-3.363$, $p=0.001$**	$Z=-10.837$, $p=0.000$**	$Z=-10.862$, $p=0.000$**
Moderate	3.82 ± 3.36; 3.00 (0–20)	5.10 ± 3.50; 4.00 (0–23)	3.60 ± 2.29; 3.00 (0–12)	χ^2 (2) = 59.491, $p=0.000$*	$Z=-5.151$, $p=0.000$**	$Z=-0.912$, $p=0.362$	$Z=-8.725$, $p=0.000$**
Minor	0.20 ± 0.53; 0.00 (0–4)	0.19 ± 0.43; 0.00 (0–2)	0.06 ± 0.24; 0.00 (0–1)	χ^2 (2) = 28.386, $p=0.000$*	$Z=-0.297$, $p=0.766$	$Z=-4.416$, $p=0.000$**	$Z=-5.231$, $p=0.000$**
Total	9.47 ± 6.07; 8.00 (2–40)	10.11 ± 6.92; 8.00 (1–37)	6.29 ± 3.66; 6.00 (1–21)	χ^2 (2) = 119.935, $p=0.000$*	$Z=-0.758$, $p=0.449$	$Z=-7.827$, $p=0.000$**	$Z=-11.040$, $p=0.000$**

*Statistically significant: $p<0.05$ (Friedman test)

**Statistically significant: $p<0.0167$ (Bonferroni correction applied for post hoc Wilcoxon tests)

Table 4 Description and frequency of Contraindicated pDDIs across phases of treatment

Combination	Possible clinical outcome	Phase: n (%)		
		First	Second	Third
Aspirin + ketorolac	↑ Gastrointestinal adverse effects (peptic ulcers, gastrointestinal bleeding, and/or perforation) and possible ↑ serum ketorolac levels	50 (20.4)	52 (21.2)	2 (0.8)
Diclofenac + ketorolac	↑ Gastrointestinal adverse effects (peptic ulcers, gastrointestinal bleeding, and/or perforation)	1 (0.4)	–	–
Atropine + potassium chloride	↑ Risk of gastrointestinal lesions	–	3 (1.2)	–
Haloperidol + metoclopramide	↑ Risk of extrapyramidal reactions and neuroleptic malignant syndrome	–	1 (0.4)	–
Metoclopramide + risperidone	↑ Risk of extrapyramidal reactions and neuroleptic malignant syndrome	–	1 (0.4)	–

↑ increased/enhanced; ↓ decreased/reduced

(first phase), obesity (first phase), systolic blood pressure at admission (first phase), TIMI risk score at admission (second phase), ALT (first phase), LDL (third phase), number of physicians who prescribed drugs to a single patient (second phase), number of prescribed drugs (all phases), ACE inhibitors (all phases), analgesics (all phases), antiarrhythmic drugs (all phases), anticoagulants (second and third phases), antidepressants (second and third phases), antidiabetics (all phases), antipsychotics (third phase), beta-blockers (all phases), bronchodilators (all phases), and diuretics (all phases).

A consistent negative association is observed for mechanical ventilation (second phase), dementia (second phase), and drug allergy noted in the medical documentation (second phase).

The effect of some predictors depends on the phase of treatment and severity of pDDIs: heart failure (positive for Moderate and Minor pDDIs in first phase, and negative for Major pDDIs in third phase), diabetes (negative for Contraindicated pDDIs in second phase and positive for Major pDDIs in first phase), and aPTT (positive for Major pDDIs in first phase and negative for Contraindicated pDDIs in second phase).

Tested interaction terms contribute to a significant increase in explained variance in two models (Supplementary Table 2). A significant positive interaction is detected between CCI and the length of hospitalization (first and third phases).

Discussion

All ACS patients are exposed to at least one pDDI in all three phases of treatment. The lowest exposure to pDDIs is detected at discharge from hospital. Age, > 6 h from the beginning of the symptoms to admission, primary PCI, STE-ACS, COPD, delirium, hyperlipidemia, hypertension, obesity, systolic blood pressure at admission, TIMI risk score at admission, ALT, LDL, number of physicians who prescribed drugs to a single patient, number of prescribed drugs, ACE inhibitors, analgesics, antiarrhythmic drugs, anticoagulants, antidepressants, antidiabetics, antipsychotics, beta-blockers,

Table 5 Risk factors for potential drug–drug interactions detected by Micromedex® across phases of treatment

Variable	First phase			Second phase			Third phase		
	B	95%CI	*p*	B	95%CI	*p*	B	95%CI	*p*
Contraindicated	*n* = 245			*n* = 245			–		
Constant	0.387	0.013; 0.762	0.043*	–	–	–	–	–	–
STE-ACS	–	–	–	0.121	0.047; 0.195	0.001*	–	–	–
Dementia	–	–	–	− 0.528	− 0.915; − 0.142	0.008*	–	–	–
Delirium	–	–	–	0.322	0.094; 0.551	0.006*	–	–	–
Hypertension	0.110	0.017; 0.203	0.021*	–	–	–	–	–	–
Diabetes	–	–	–	− 0.121	− 0.219; − 0.023	0.016*	–	–	–
Obesity	0.212	0.062; 0.362	0.006*	–	–	–	–	–	–
aPTT	–	–	–	− 0.004	− 0.007; 0.000	0.024*	–	–	–
Primary PCI	0.113	0.017; 0.208	0.022*	–	–	–	–	–	–
Mechanical ventilation	–	–	–	− 0.313	− 0.565; − 0.061	0.015*	–	–	–
Analgesics	0.720	0.638; 0.802	0.000*	0.731	0.647; 0.815	0.000*	–	–	–
R^2; *F* (*p*)	0.630; 19.057 (0.000*)			0.668; 26.844 (0.000*)			–		
Major	*n* = 245			*n* = 245			*n* = 245		
Constant	− 2.907	− 5.504; − 0.311	0.028*	–	–	–	–	–	–
Heart failure	–	–	–	–	–	–	− 1.012	− 1.901; − 0.122	0.026*
Diabetes	0.827	0.114; 1.539	0.023*	–	–	–	–	–	–
aPTT	0.056	0.033; 0.079	0.000*	–	–	–	–	–	–
ALT	0.012	0.003; 0.020	0.007*	–	–	–	–	–	–
TIMI risk score at admission	–	–	–	0.259	0.034; 0.484	0.024*	–	–	–
Primary PCI	0.963	0.265; 1.661	0.007*	–	–	–	–	–	–
Number of prescribed drugs	0.250	0.159; 0.340	0.000*	0.292	0.184; 0.399	0.000*	0.215	0.142; 0.288	0.000*
Antiarrhythmic drugs	0.818	0.202; 1.433	0.009*	1.075	0.213; 1.937	0.015*	0.926	0.406; 1.446	0.001*
Antidiabetics	–	–	–	–	–	–	0.548	0.021; 1.076	0.042*
Antidepressants	–	–	–	2.117	0.287; 3.947	0.024*	1.856	0.806; 2.905	0.001*
Anticoagulants	–	–	–	1.157	0.489; 1.824	0.001*	1.143	0.683; 1.604	0.000*
Analgesics	2.393	1.803; 2.983	0.000*	2.270	1.575; 2.966	0.000*	–	–	–
Diuretics	1.349	0.692; 2.006	0.000*	1.851	1.169; 2.534	0.000*	1.458	1.100; 1.816	0.000*
Antipsychotics	–	–	–	–	–	–	1.736	0.358; 3.113	0.014*
R^2; *F* (*p*)	0.637; 19.661 (0.000*)			0.692; 22.670 (0.000*)			0.650; 23.304 (0.000*)		
Moderate	*n* = 245			*n* = 245			*n* = 245		
Constant	− 4.248	− 7.099; − 1.397	0.004*	− 2.423	− 4.374; − 0.471	0.015*	− 3.852	− 5.391; − 2.314	0.000*
Age	–	–	–	–	–	–	0.023	0.003; 0.043	0.025*
Heart failure	1.728	0.396; 3.060	0.011*	–	–	–	–	–	–
COPD	1.082	0.238; 1.927	0.012*	–	–	–	–	–	–

Table 5 (continued)

Variable	First phase			Second phase			Third phase		
	B	95%CI	*p*	B	95%CI	*p*	B	95%CI	*p*
Systolic BP at admission	0.012	0.004; 0.020	0.003*	–	–	–	–	–	–
LDL	–	–	–	–	–	–	0.163	0.014; 0.313	0.032*
Drug allergy noted in the medical documentation	–	–	–	− 0.784	− 1.391; − 0.177	0.012*	–	–	–
Number of prescribed drugs	0.350	0.271; 0.428	0.000*	0.377	0.306; 0.448	0.000*	0.259	0.188; 0.329	0.000*
Antiarrhythmic drugs	–	–	–	2.025	1.401; 2.650	0.000*	1.343	0.738; 1.947	0.000*
Antidiabetics	1.681	0.902; 2.460	0.000*	2.525	1.803; 3.247	0.000*	2.664	2.073; 3.255	0.000*
Analgesics	–	–	–	–	–	–	1.547	0.368; 2.725	0.010*
ACE inhibitors	0.876	0.328; 1.423	0.002*	1.588	1.049; 2.128	0.000*	1.002	0.596; 1.408	0.000*
Beta-blockers	1.419	0.915; 1.922	0.000*	1.310	0.806; 1.815	0.000*	1.023	0.637; 1.408	0.000*
Diuretics	1.139	0.586; 1.692	0.000*	–	–	–	–	–	–
R^2; *F* (*p*)	0.802; 43.014 (0.000*)			0.803; 48.302 (0.000*)			0.723; 34.767 (0.000*)		
Minor	*n* = 245			*n* = 245			*n* = 245		
Constant	− 0.582	− 1.088; − 0.075	0.025*	–	–	–	–	–	–
> 6 h from the beginning of the symptoms to admission	0.152	0.039; 0.265	0.008*	–	–	–	–	–	–
Heart failure	0.635	0.293; 0.977	0.000*	–	–	–	–	–	–
TIMI risk score at admission	–	–	–	0.035	0.006; 0.065	0.019*	–	–	–
Hyperlipidemia	0.216	0.090; 0.342	0.001*	–	–	–	0.046	0.002; 0.091	0.040*
Number of physicians who prescribed drugs to a single patient	–	–	–	0.054	0.008; 0.099	0.021*	–	–	–
Number of prescribed drugs	0.046	0.029; 0.063	0.000*	0.025	0.012; 0.037	0.000*	–	–	–
Bronchodilators	0.651	0.441; 0.862	0.000*	0.570	0.429; 0.711	0.000*	0.657	0.576; 0.738	0.000*
R^2; *F* (*p*)	0.481; 10.390 (0.000*)			0.599; 18.787 (0.000*)			0.666; 30.433 (0.000*)		

Complete list of variables entered in block 1 and 2 of hierarchical multiple linear regression analysis is provided in Supplementary Text 1 in Electronic Supplementary Material

B unstandardized coefficient, *CI* confidence interval, *p* statistical significance, * statistically significant ($p < 0.05$)

bronchodilators, and diuretics seem to increase the risk of pDDIs in ACS patients. On the other hand, mechanical ventilation, dementia, and drug allergy noted in the medical documentation seem to protect against them. Effects of heart failure, diabetes, and aPTT depend on the phase of treatment and severity of pDDI. In addition, a significant positive interaction is detected between CCI and the length of hospitalization.

A previous study detects at least one pDDI in 99% of ACS patients' prescriptions [15], which concurs with our findings. The pharmacotherapy of ACS is complex and multiple drugs across different phases of treatment are needed to achieve an adequate clinical outcome [2, 3, 5]. Concurrent prescribing of antiplatelet therapy, ACE inhibitor or angiotensin II receptor blocker, beta-blocker, and statin at hospital discharge is associated with lower all-cause mortality that persists for up to 12 months after discharge [18], while, in ACS patients undergoing PCI, periprocedural loading doses of statins, like atorvastatin, seem to reduce the rate of major adverse cardiovascular events at 30 days, primarily in STEMI patients [19]. However, a higher number of prescribed drugs is associated with a significantly increased risk of pDDIs in many studies [7–15], including ours. The average total number of pDDIs is highest in second phase (after coronary angiography was performed up to the last day of hospitalization). However, a significant difference is observed only between first and third and second and third phases, but not between first and second phases. Vonbach et al. reported a significantly higher number of pDDIs during hospitalization compared to admission and discharge in patients hospitalized at internal medicine department, which is likely a consequence of a higher number of prescribed drugs during hospitalization [20]. The different observation of our study might be explained by differences in study population, design, and used interaction checkers.

A longer hospitalization is associated with an increased risk of pDDIs in many previous studies [7, 9, 10, 12, 13, 15], while some report an increased risk with multimorbidity [7, 13]. We observe a significant positive interaction between these two predictors in first and third phases of treatment. It seems that the chance of getting multiple drugs increases with a longer hospital stay and number of comorbidities, consequently, increasing the risk of pDDIs. More physicians involved in prescribing drugs increase the risk of pDDIs during second phase. In the hospital setting, physicians seem to focus on their own therapeutic area, which may increase exposure to pDDIs [21].

Obesity, heart failure, COPD and bronchodilators use, diabetes and antidiabetics use, hypertension and higher systolic blood pressure at admission, as well as hyperlipidemia and higher LDL and ALT are all associated with a higher number of pDDIs in our study. Obese and diabetic patients have a higher incidence of other comorbidities and cardiovascular risk factors requiring multiple drug therapy [22, 23], which puts them at a higher risk of pDDIs. Similarly, this is true for high-risk populations with increased mortality rates, like ACS patients with heart failure or COPD [23, 24]. However, some comorbidities seem to protect from certain pDDIs: diabetes from Contraindicated pDDIs in second phase and heart failure from Major pDDIs in third phase. A possible explanation is that physicians pay more attention to these high-risk patients to avoid unnecessary medications and pDDIs.

A higher TIMI risk score at admission is associated with an increased risk of pDDIs during second phase. This might be attributed to its high specificity to predict 30-day adverse outcomes following ACS [25]. In addition, > 6 h from the beginning of the symptoms to admission is also associated with the increased risk of pDDIs in first phase. Late ACS presenters (> 6 h postsymptom onset) have a higher rate of adverse outcomes [26], which suggests that these patients require more drugs, and are thus exposed to higher number of pDDIs.

Results regarding the association of age with pDDIs are inconsistent. Some studies, like ours, report a significant positive association between age and pDDIs [8, 9, 11, 12, 14], while others do not [7]. Older patients usually have more comorbidities, which in turn lead to multiple drug therapy and increase the risk of pDDIs [10, 12, 23].

An increased risk of bleeding is most common potential clinical outcome of pDDIs detected from the point of first medical contact to coronary angiography. This is expected as the current guidelines recommend starting all patients without contraindications on parenteral anticoagulant as soon as possible after the initial presentation in addition to antiplatelet therapy, and discontinuing anticoagulants after PCI, unless otherwise indicated [1–3]. Primary PCI significantly increases the risk of pDDIs in first phase. Dual antiplatelet therapy, which is essential to immediate and extended interventional success, particularly contributes to pDDIs in ACS patients undergoing PCI [27]. Interestingly, aPTT is associated with an increased risk of pDDIs in first phase of treatment, which might be a consequence of high use of parenteral anticoagulants in this treatment phase. On the other hand, higher baseline aPTT acts protectively in second phase of treatment, suggesting that physicians are more cautious in these patients. The effects on the cardiovascular system are most common after coronary angiography and at discharge from hospital. These effects are possible clinical outcomes of pDDIs of drugs with an important role in secondary prevention: beta-blockers, ACE inhibitors, and diuretics [1], which are identified as independent risk factors for pDDIs in our study.

Analgesics increase the risk of pDDIs across all the phases of treatment. About 28% of patients are prescribed analgesics in the first two phases of treatment, and about

20% of them are prescribed ketorolac, a nonsteroidal anti-inflammatory drug (NSAID). These patients are exposed to its contraindicated potential interaction with aspirin, which may increase the risk of gastrointestinal bleeding. Concomitant use of ketorolac with the other antiplatelet drugs, anticoagulants, and corticosteroids may also increase the risk of gastrointestinal bleeding. Considering their interactions and association with other adverse outcomes, NSAIDs (except aspirin) should not be used in ACS patients [28, 29]. Intravenous opioids (e.g., morphine) that are recommended for pain relief by the current ACS guidelines [2, 3] were prescribed to a minority of patients in our study. In general, prescribing of opioids in Serbia is lower compared to other countries probably because of the fear of their potential side effects and addictive potential [30], while ketorolac might be a favourite NSAID due to its ability to rapidly and potently relieve pain [29]. Morphine may also interact with the other drugs used in ACS treatment [2, 3]. It may delay onset of action and diminish effects of oral antiplatelets, which might result in the early treatment failure in susceptible patients [2, 3].

STE-ACS patients have an increased risk of Contraindicated pDDIs in second phase. As previously mentioned, the most common contraindicated potential interaction involves the analgesic: ketorolac. STE-ACS occurs when there is a complete vessel occlusion, while NSTE-ACS is a result of subtotal occlusion [28], so STE-ACS patients may have a higher level of pain, thus, having a higher need for an analgesic, which exposes them to a higher risk of this pDDI.

Drugs affecting the central nervous system (antidepressants and antipsychotics) significantly contribute to the number of pDDIs in our study. Antidepressant use has increased considerably in ACS patients, raising the possibility that they are being used by some patients who may not benefit meaningfully in addition to being exposed to significant DDIs [31]. Antidepressants may prolong the QT interval [32]. This effect may be even more profound when combined with other QT interval prolonging drugs including antipsychotics, antibiotics, and antiarrhythmic drugs [32]. Antiarrhythmic drugs are independent predictors of the number of pDDIs in our patients, as well. Furthermore, selective serotonin reuptake inhibitors combined with antiplatelets and anticoagulants may increase the risk of bleeding [33, 34]. Therefore, careful consideration needs to be given to balance between potential benefits and harms when prescribing antidepressants and antipsychotics to ACS patients [31, 35].

ACS patients with cognitive impairment or impaired consciousness, i.e., patients with dementia and mechanical ventilation have lower risk of pDDIs in our study. It was previously observed that use of cardiovascular pharmacotherapy (e.g., aspirin, P2Y12 inhibitors, and beta-blockers) and reperfusion therapy is less common in patients with acute myocardial infarction treated with mechanical ventilation [36]. Drug contraindications associated with acute comorbidities may lead to less common use of cardiovascular pharmacotherapy in mechanically ventilated patients, while lower use of reperfusion therapy might be attributed to delayed admission that might contraindicate reperfusion in STEMI patients [36]. In addition, mechanically ventilated patients generally require more resources [37], which may involve more physician attention, as well. Therefore, the protective effect of mechanical ventilation on the occurrence of pDDIs might be explained by a lower number of prescribed drugs and vigilance of physicians when prescribing drugs. It was reported that cognitive impairment may protect intensive-care unit (ICU) patients from pDDIs with the possible explanation that physicians take over complete responsibility for prescribing to cognitively impaired patients [38]. On the other hand, delirium increases the risk of pDDIs in second phase. Since delirium is a transient cause of cerebral dysfunction [39], it is not unexpected that the risk of pDDIs is increased during hospitalization when patients are usually prescribed antipsychotics that may interact with other drugs.

Several take home messages can be derived from our results. Above all, physicians should be vigilant to the possibility of pDDIs particularly in the subsets of patients harbouring factors that may increase their rate. In first treatment phase, the risk of pDDI seems to be higher in patients admitted > 6 h from the beginning of the symptoms, undergoing primary PCI, with higher systolic blood pressure at admission, ALT and aPTT, multiple comorbidities (e.g., COPD, heart failure, diabetes, hyperlipidemia, hypertension, and obesity), who are likely to be hospitalized longer and are prescribed multiple drugs, so pDDI screening should be performed in patients with these characteristics. In second treatment phase, this should be done in patients with STE-ACS, delirium, and higher TIMI risk score at admission, who are prescribed multiple drugs by multiple physicians. At discharge, screening for pDDIs should be performed in older patients, with multiple comorbidities, hyperlipidemia, and higher LDL, who have been hospitalized longer and are prescribed multiple drugs. Drugs associated with a higher number of pDDIs to which particular attention should be paid are: antidepressants, antipsychotics, analgesics, antiarrhythmic drugs, anticoagulants, antidiabetics, ACE inhibitors, beta-blockers, bronchodilators, and diuretics. Risk of pDDIs in ACS patients seems to be higher compared to the general patient population on medical wards and ICU. Up to 100% of ACS patients may be exposed to at least one pDDI, while about 33% of general patients and 67% of ICU patients may experience a pDDI during their hospital stay [40]. Some risk factors for pDDIs in ACS patients are similar to general patient population (e.g., older age and higher number of prescribed drugs [41]), but, in ACS patients, there are some disease-specific risk factors, as well (e.g., type of ACS and TIMI risk score).

Our work has some limitations that need to be considered. First, the study is unicentric, which might have introduced a bias of local and national quality of medical education in the results. In addition, we analyzed only potential DDIs. Their clinical outcomes could not be followed in our study, which is another limitation. Actual DDIs can be difficult to identify [27]. Although altered concentrations of drugs can be objectively measured for most of the drugs in research setting, it is more difficult to describe their clinical impact [27], and many factors (such as concomitant disease or genetic predisposition) make the causality assessment of the interaction difficult [42]. In addition, measurement of residual platelet reactivity was not performed in our patients, so we were not able to evaluate their thrombotic and bleeding risk with regard to antiplatelet therapy. Despite these limitations, the findings of our study could serve as a useful input for understanding the extent of the problem, and taking measures to improve the management of DDIs in ACS patients.

Conclusion

The lowest exposure to pDDIs is detected at discharge from hospital. Age, > 6 h from the beginning of the symptoms to admission, primary PCI, STE-ACS, COPD, delirium, hyperlipidemia, hypertension, obesity, systolic blood pressure at admission, TIMI risk score at admission, ALT, LDL, number of physicians who prescribed drugs to a single patient, number of prescribed drugs, and prescribing of certain pharmacological classes seem to increase risk of pDDIs in ACS patients. On the other hand, mechanical ventilation, dementia, and drug allergy noted in the medical documentation seem to protect against them. Effects of heart failure, diabetes, and aPTT depend on the phase of treatment and severity of pDDI. Physicians should pay more attention to the possibility of pDDIs in patients harbouring factors that may increase their rate.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights The Ethics Committee of the Clinical Centre Kragujevac approved the study prior to its initiation. All procedures performed in studies involving human participants are in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This is a retrospective study, and for this type of study, formal consent is not required.

Data availability statement The data sets generated during or analyzed during the current study are available from the corresponding author on reasonable request.

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