

DRUG-DRUG INTERACTIONS IN ACUTE CORONARY SYNDROME PATIENTS: SYSTEMATIC REVIEW

Ana V. Pejčić^{1,2}, Slobodan M. Janković², Goran Davidović³

¹University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacy, Kragujevac, Serbia

²University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacology and Toxicology, Kragujevac, Serbia

³University of Kragujevac, Faculty of Medical Sciences, Department of Internal Medicine, Kragujevac, Serbia

INTERAKCIJE IZMEĐU LEKOVA KOD BOLESNIKA SA AKUTNIM KORONARNIM SINDROMOM: SISTEMATSKI PREGLED LITERATURE

Ana V. Pejčić^{1,2}, Slobodan M. Janković², Goran Davidović³

¹Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za farmaciju, Kragujevac, Srbija

²Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za farmakologiju i toksikologiju, Kragujevac, Srbija

³Univerzitet u Kragujevcu, Fakultet medicinskih nauka, Katedra za internu medicinu, Kragujevac, Srbija

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ABSTRACT

Drug-drug interaction (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 result in a precipitation of an adverse event or alteration of its therapeutic effects. The aim of this systematic review was to provide an overview of DDIs that were actually observed or evaluated in acute coronary syndrome (ACS) patients with particular focus on DDIs with clinical relevance. Electronic searches of the literature were conducted in the following databases: MEDLINE, EBSCO, Scopus, Google Scholar and SCIndeks. A total of 117 articles were included in the review. This review showed that ACS patients can be exposed to a variety of DDIs with diverse outcomes which include decreased efficacy of antiplatelet drugs, thrombolytics or anticoagulants, increased risk of bleeding, rhabdomyolysis, hepatotoxicity, adverse effects on cardiovascular system (e.g. QT interval prolongation, arrhythmias, excessive bradycardia, severe hypotension), serotonin syndrome and drug-induced fever. Majority of the DDIs involved antiplatelet drugs (e.g. aspirin, clopidogrel and ticagrelor). Evidence of some of the reported DDIs is inconclusive as some of the studies have shown conflicting results. There is a need for additional post-marketing and population-based studies to evaluate the true effects of disease states and other factors on the clinical outcomes of DDIs. Clinicians should be attentive to the potential for DDIs and their associated harm in order to minimize or, if possible, avoid medication-related adverse events in ACS patients.

Keywords: drug-drug interactions, acute coronary syndrome, review

SAŽETAK

Interakcija između lekova predstavlja klinički značajnu promenu u izloženosti i/ili odgovoru na lek koja je izazvana istovremenom primenom drugog leka, a koja za posledicu može imati pojavu neželjenih efekata ili izmenu terapijskog efekta. Cilj ovog sistematskog pregleda literature bio je da pruži pregled interakcija između lekova koje su se zaista dogodile ili koje su bile ispitivane u populaciji bolesnika sa akutnim koronarnim sindromom (AKS) sa posebnim osvrtom na klinički značajne interakcije. Elektronsko pretraživanje literature je sprovedeno u sledećim bazama podataka: MEDLINE, EBSCO, Scopus, Google Scholar i SCIndeks. U sistematski pregled literature uključeno je ukupno 117 publikacija. Pregled literature je pokazao da bolesnici sa AKS mogu biti izloženi različitim interakcijama između lekova sa raznovrsnim ishodima koji uključuju smanjenu efikasnost antiagregacionih lekova, trombolitika i antikoagulanasa, povećan rizik za pojavu krvarenja, rhabdomiolizu, hepatotoksičnost, neželjene efekte na kardiovaskularni sistem (npr. produženje QT intervala, aritmije, teška bradikardija i hipotenzija), serotoniniski sindrom i visoku temperaturu uzrokovanu primenom lekova. Većina interakcija je uključivala antiagregacione lekove (npr. aspirin, klopidogrel i tikagrelor). Dokazi za postojanje nekih interakcija nisu saglasni, s obzirom na to da su neke studije pokazale kontradiktorne rezultate. Postoji potreba za sprovođenjem dodatnih postmarketinških i populacionih studija kako bi se utvrdio stvarni uticaj bolesti i drugih faktora na kliničke ishode interakcija između lekova. Lekari bi trebalo da obrate pažnju na mogućnost pojave interakcija između lekova i njihove moguće štetne posledice, kako bi smanjili, ili ako je moguće, sprečili neželjene događaje uzrokovane lekovima u populaciji bolesnika sa AKS.

Ključne reči: interakcije između lekova, akutni koronarni sindrom, pregled literature



ABBREVIATIONS

ACE – Angiotensin-converting enzyme	NSAID(s) – Non-steroidal anti-inflammatory drug(s)
ACS – Acute coronary syndrome	NSTEMI – Non-ST-segment elevation myocardial infarction
AHA – American Heart Association	PCI – Percutaneous coronary intervention
CCB(s) – Calcium channel blocker(s)	PPI(s) – Proton pump inhibitor(s)
CYP – Cytochrome P450	rTPA – Recombinant tissue-type plasminogen activator
DAPT – Dual antiplatelet therapy	SSRI(s) – Selective serotonin reuptake inhibitor(s)
DDI(s) – Drug-drug interaction(s)	STEMI – ST-segment elevation myocardial infarction
ESC – European Society of Cardiology	
GP – Glycoprotein	
NNH – Number needed to harm	

INTRODUCTION

Acute coronary syndrome (ACS) is a high-risk manifestation of coronary artery disease associated with the rupture of an atherosclerotic plaque and partial or complete thrombosis of the coronary artery (1-3). Clinical manifestations of ACS include ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris (4). Initial and long-term treatment of ACS involves multiple medications such as antiplatelet drugs, anticoagulants, analgesics, nitrates, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and lipid-lowering therapy (5-7). Additionally, ACS patients often have other comorbidities requiring long-term treatment which put them in high risk of drug-drug interactions (DDIs) (5-7).

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 result in a precipitation of an adverse event or alteration of its therapeutic effects (8, 9). Potential DDI is defined as a co-prescription or co-administration of two drugs known to interact (8). Studies have shown that about 99-100% of ACS patients are exposed to at least one potential DDI during different phases of treatment (10, 11). DDIs may have important implications in the setting of ACS, particularly because they may affect the balance of preventing thrombotic events versus the potential for increased bleeding risk (12). Although, there are many interaction checkers available, they have limited clinical utility (13), so it is important that prescribers are aware of the potential DDIs and associated harm in order to minimize or, if possible, avoid medication-related adverse events, decrease risk of hospitalization or longer hospital stay (14).

Previous systematic reviews have either focused only on the DDIs in the setting of ACS and dual antiplatelet therapy (DAPT) (5) or on the DDIs that have the potential to affect procedural outcomes of cardiovascular catheterizations and interventions with only a brief discussion of other DDIs that are highly likely in the coronary artery disease patients (12).

Therefore, the aim of this systematic review was to provide an overview of DDIs that were actually observed or evaluated in ACS patients with particular focus on DDIs with clinical relevance.

METHODS

Electronic searches of the literature were conducted in the following online databases: MEDLINE available at <https://www.ncbi.nlm.nih.gov/pubmed/>, EBSCO available at <https://ezproxy.nb.rs:2443/kobson.82.html>, Scopus available at <https://www.scopus.com>, Google Scholar available at <https://scholar.google.com/> and Serbian Citation Index (SCIndeks) available at <https://scindeks.ceon.rs/>.

The search and evaluation of the retrieved articles was performed from April 1st to April 17th, 2019. Details of the search strategies for each database are provided in Table 1. Inclusion criteria were: clinical trials or observational studies or case series or case reports which included patients with one of the manifestations of the ACS (unstable angina pectoris, myocardial infarction with or without ST-segment elevation) and which aimed to investigate or report a clinically relevant DDI. Exclusion criteria were: systematic reviews, meta-analysis, expert opinions, guidelines, “in vitro” studies, studies conducted on animals. There were no restrictions on publication date, format or language in the search strategy. The references of the retrieved articles were also searched for further similar studies.

A clinically relevant DDI for the purpose of this study was defined as a DDI that could be associated with any of the following: clinical or laboratory signs of toxicity causally associated with the concomitant administration of the combination of drugs (as estimated by the authors of the respective study); loss of efficacy of one or both drugs from the drug combination believed to be caused by an interaction between them (as estimated by the authors of the respective study); or change of the drug therapy because of the recognition of a DDI with adverse consequences.



Table 1. Search strategy for databases

Database	Search strategy
MEDLINE	((("drug interactions"[MeSH Terms] OR ("drug"[All Fields] AND "interactions"[All Fields]) OR "drug interactions"[All Fields] OR ("drug"[All Fields] AND "interaction"[All Fields]) OR "drug interaction"[All Fields]) OR ("drug interactions"[MeSH Terms] OR ("drug"[All Fields] AND "interactions"[All Fields]) OR "drug interactions"[All Fields]) OR ("drug interactions"[MeSH Terms] OR ("drug"[All Fields] AND "interactions"[All Fields]) OR "drug interactions"[All Fields] OR ("drug"[All Fields] AND "drug"[All Fields] AND "interaction"[All Fields]) OR "drug drug interaction"[All Fields]) OR (drug-drug[All Fields] AND interactions[All Fields]) OR (drug[All Fields] AND co-administration[All Fields])) AND ((("acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields] AND "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields]) OR ("st elevation myocardial infarction"[MeSH Terms] OR ("st"[All Fields] AND "elevation"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "st elevation myocardial infarction"[All Fields] OR "stemi"[All Fields]) OR ("non-st elevated myocardial infarction"[MeSH Terms] OR ("non-st"[All Fields] AND "elevated"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "non-st elevated myocardial infarction"[All Fields] OR "nSTEMI"[All Fields]) OR ("angina, unstable"[MeSH Terms] OR ("angina"[All Fields] AND "unstable"[All Fields]) OR "unstable angina"[All Fields] OR ("unstable"[All Fields] AND "angina"[All Fields] AND "pectoris"[All Fields]) OR "unstable angina pectoris"[All Fields]) OR "myocardial infarction"[ti]) NOT (("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]) OR ("meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]) OR "in vitro"[All Fields] OR ("animals"[MeSH Terms:noexp] OR animal[All Fields]))
EBSCO	SU (((drug interaction) OR (drug interactions) OR (drug-drug interaction) OR (drug-drug interactions) OR (drug co-administration)) AND ((acute coronary syndrome) OR (STEMI) OR (NSTEMI) OR (unstable angina pectoris) OR (TI "myocardial infarction")) NOT (review OR meta-analysis OR "in vitro" OR animal)) OR AB (((drug interaction) OR (drug interactions) OR (drug-drug interaction) OR (drug-drug interactions) OR (drug co-administration)) AND ((acute coronary syndrome) OR (STEMI) OR (NSTEMI) OR (unstable angina pectoris) OR (TI "myocardial infarction")) NOT (review OR meta-analysis OR "in vitro" OR animal))
Scopus	(((drug AND interaction) OR (drug AND interactions) OR (drug-drug AND interaction) OR (drug-drug AND interactions) OR (drug AND co-administration)) AND ((acute AND coronary AND syndrome) OR (stemi) OR (nstemi) OR (unstable AND angina AND pectoris) OR TITLE ("myocardial infarction")) AND NOT (review OR meta-analysis OR "in vitro" OR animal)
SCIndeks	(ARTAK: ((drug interaction) OR (drug interactions) OR (drug-drug interactions) OR (drug-drug interaction) OR (co-administration) OR (combined therapy)) AND ((acute coronary syndrome) OR (STEMI) OR (NSTEMI) OR (myocardial infarction) OR (unstable angina pectoris)))
Google Scholar	drug interaction drug-drug interactions coadministration "acute coronary syndrome" OR STEMI OR NSTEMI OR "unstable angina" OR "myocardial infarction" -review -"meta-analysis" -animal -"in vitro"

RESULTS

Results of the literature search are shown in Figure 1. A total of 117 articles were included in this systematic review. An overview of drug combinations involved in DDIs in ACS patients and their possible outcomes is provided in Table 2.

DDIs leading to decreased efficacy of antiplatelet drugs

Morphine and antiplatelet drugs. Morphine use in ACS patients was associated with a delayed onset of action of oral antiplatelet agents: clopidogrel (15), prasugrel (15-18) and ticagrelor (16, 17, 19-21) probably due to a delay in drug absorption as a result of inhibition of gastrointestinal motility and gastric emptying. Also, STEMI patients who received morphine with ticagrelor had a less favorable ischemic

outcome (22). In addition, morphine co-administration in STEMI patients who received DAPT (aspirin with clopidogrel or ticagrelor), was associated with impaired thrombotic status at presentation, reduced spontaneous myocardial reperfusion (before primary percutaneous coronary intervention (PCI)) and larger infarct size (23).

Acid-suppressive drugs and antiplatelet drugs. Clopidogrel is a prodrug which requires conversion via cytochrome P450 (CYP) system (dominantly by CYP3A4, CYP3A5 and CYP2C19) before the desired clinical effect is achieved (24-35). Drugs that interfere with or are co-metabolized via those enzymes might decrease its antiplatelet effect and increase the risk of thrombotic events (24-35). Proton pump inhibitors (PPIs) are metabolized by CYP enzymes, leading to a potential inhibition of CYP2C19 (24-35).



Figure 1. Selection of studies

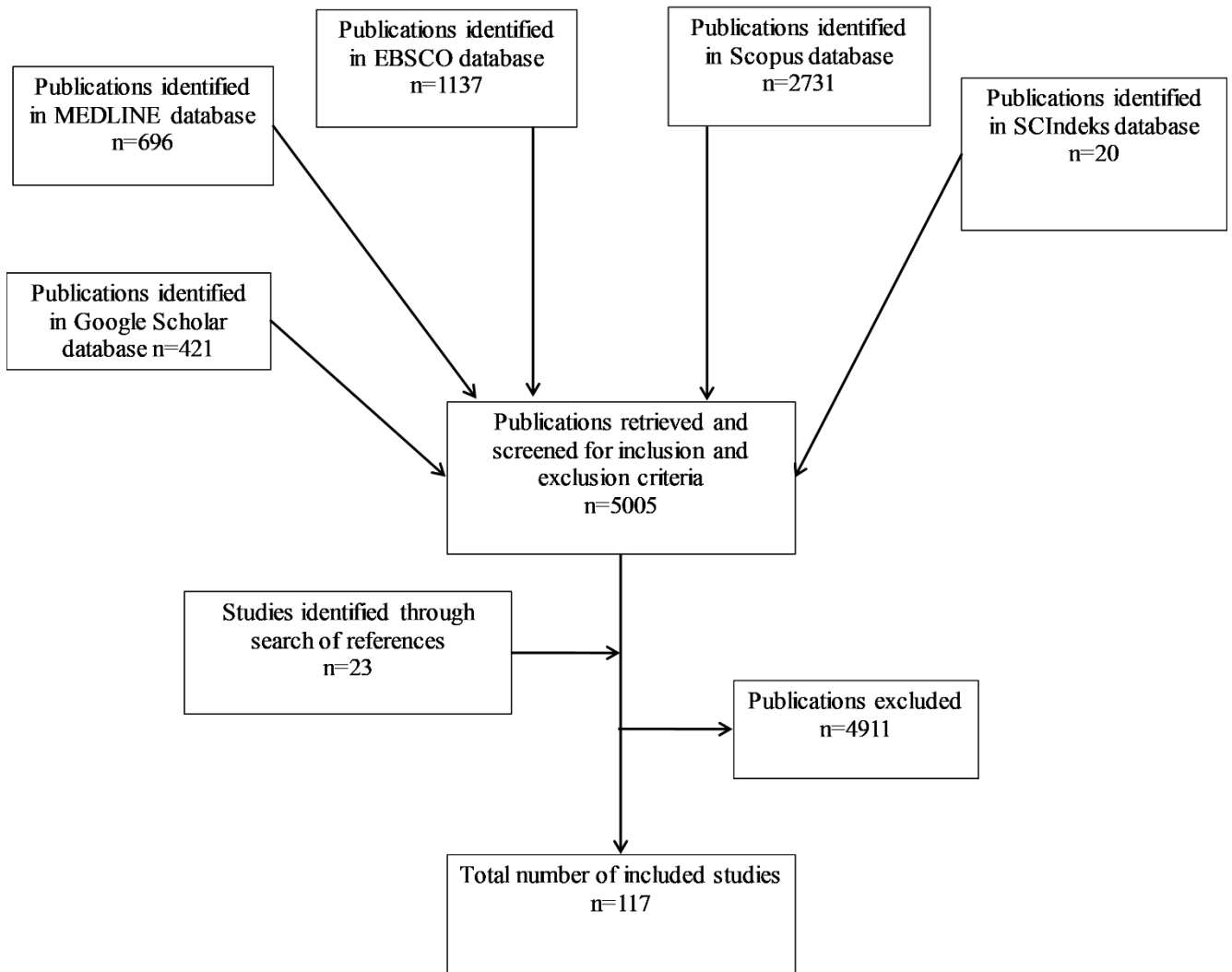


Table 2. An overview of drug combinations involved in DDIs and their possible outcomes in ACS patients

Drug combination	Description
Amiodarone + antiretroviral drugs	Acquired long QT syndrome and torsades de pointes cardiac arrest (122).
Amiodarone + sofosbuvir + daclatasvir	Syncope, extreme bradycardia and cardiac asystole (123).
Anticoagulants + thrombolytics	Increased risk of bleeding (99).
Antiplatelet drugs (combinations)	Increased risk of bleeding (82-89).
Antiplatelet drugs + anticoagulants	Increased risk of bleeding (91-97).
Antiplatelet drugs + anticoagulant + thrombolytic	Increased risk of bleeding (100).
Antiplatelet drugs + morphine	Delayed onset of action of oral antiplatelet drugs (e.g. clopidogrel (15), prasugrel (15-18), ticagrelor (16, 17, 19-21)), less favorable ischemic outcome with ticagrelor (22), impaired thrombotic status at presentation (aspirin with clopidogrel or ticagrelor) (23).
Antiplatelet drugs + NSAID + corticosteroid	Increased risk of bleeding (101)
Antiplatelet drugs + SSRIs	Increased risk of bleeding (102)
Antiplatelet drugs + thrombolytics	Increased risk of bleeding (98, 99).
Antithrombotic therapy + NSAIDs	Increased risk of excess thrombotic events and bleeding (62).



Drug combination	Description
Aspirin + ACE inhibitors	Antagonized effects of ACE inhibitors (125) (no negative interaction in (126-129)).
Aspirin + ibuprofen	Increased rate of recurrent acute myocardial infarction (61) (not confirmed in (63)).
Aspirin + PPIs	Increased risk of an adverse cardiovascular event (59) or enhanced antiplatelet effects of enteric-coated aspirin (60).
Carvedilol + dobutamine	Severe hypotension (118).
Clonidine + duloxetine + atorvastatin	Unexplained high fever (131).
Clopidogrel + ACE inhibitors	Increased risk of bleeding (107).
Clopidogrel + aprotinin	Reduced antiplatelet effect of clopidogrel (64).
Clopidogrel + atorvastatin	Hepatotoxicity (68, 116).
Clopidogrel + calcium channel blockers	Increased risk of ACS re-hospitalization in ACS patients not compliant to guideline-recommended secondary prevention drugs (65) (interaction not confirmed in (66, 67)).
Clopidogrel + cimetidine	Increased risk of re-infarction (28).
Clopidogrel + PPIs	Reduced antiplatelet effects (36-42) (not confirmed for all PPIs in (39, 43-47)) and increased risk of adverse cardiovascular events (24-35, 48, 49) (not confirmed for all PPIs in (40, 43, 48, 50-56)).
Escitalopram + lansoprazole	QT interval prolongation and ventricular fibrillation (117).
Escitalopram + methylene blue	Serotonin syndrome (130).
Metoprolol + cocaine	Exacerbated coronary vasoconstriction, crushing substernal chest pain, pulseless electrical activity and death (119).
Metoprolol + CYP2D6 inhibitors (e.g. paroxetine, terbinafine)	Excessive bradycardia or severe hypotension (120, 121).
Mexiletine + theophylline	Ventricular arrhythmias (124).
Nitroglycerin + heparin	Heparin resistance and attenuated anticoagulant effect (78, 79) (not confirmed in (80, 81)).
Nitroglycerin + rTPA	Reduced thrombolytic efficacy of rTPA (76, 77).
Rivaroxaban + simvastatin	Bleeding (103).
Simvastatin + diltiazem	Rhabdomyolysis (115).
Statins + fibrates	Rhabdomyolysis (113, 114).
Ticagrelor + antiepileptic CYP3A inducers (e.g. phenytoin, carbamazepine, phenobarbital)	Reduced antiplatelet effects of ticagrelor (75).
Ticagrelor + cyclosporine	Increased exposure to both drugs with increased risk of bleeding and increased cyclosporine trough concentration (105, 106).
Ticagrelor + statins (e.g. atorvastatin, simvastatin, rosuvastatin)	Rhabdomyolysis (108-112).
Warfarin + ritonavir	Removal of ritonavir led to the increase in warfarin effect (104).
Abbreviations: ACE – Angiotensin-converting enzyme; NSAID(s) – Non-steroidal anti-inflammatory drug(s); PPI(s) – Proton pump inhibitor(s); rTPA – Recombinant tissue-type plasminogen activator; SSRI(s) – Selective serotonin reuptake inhibitor(s).	

However, results of the clinical studies have shown conflicting results regarding PPIs influence on antiplatelet effects of clopidogrel and risk of adverse cardiovascular events in ACS patients. There are some studies which suggest that pantoprazole (36), esomeprazole (37) and omeprazole (38-40) may reduce antiplatelet effect of clopidogrel, and that PPIs as a group may reduce antiplatelet effects of thienopyridines (clopidogrel or ticlopidine) (41). One study showed that the degree of the interaction between clopidogrel and PPIs is not homogeneous within the class of PPIs and is less marked with pantoprazole than with omeprazole (42). On the other hand, some studies suggested that pantoprazole (39), lansoprazole (43), esomeprazole (44), rabeprazole (44) and omeprazole (45, 46) do not reduce antiplatelet effect of clopidogrel and that pantoprazole does not interfere with antiplatelet effect of P2Y₁₂ inhibitors (clopidogrel, ticagrelor, prasugrel) (47). In numerous studies concomitant use of

clopidogrel and PPIs as a group (24-35), as well as some of the individual PPIs (omeprazole (48, 49), esomeprazole (49)), was associated with a significant increase in risk of adverse cardiovascular events. In one of these studies, a similar association was observed between cardiovascular events and PPI use during ticagrelor treatment and with other non-PPI gastrointestinal treatment, suggesting that the association between PPI use and adverse events may be due to confounding, with PPI use more of a marker for, than a cause of, higher rates of cardiovascular events (33). Also, in one of the studies use of PPIs did not significantly affect the comparative effectiveness of prasugrel versus clopidogrel (34). In one study risk of rehospitalization among PPI users varied by CYP2C19 genotype, with the greatest increase in risk observed among carriers of the CYP2C19*17 allele (31). However, some studies didn't show significant influence of PPIs as a group (50-54) or individual PPIs (lansoprazole (43, 48),



omeprazole (40, 55, 56), esomeprazole (48), rabeprazole (48), pantoprazole (48)) on risk of adverse cardiovascular events in patients with ACS treated with clopidogrel. Also, in one of the studies pantoprazole did not have significant effects on the incidence of hospital-acquired pneumonia and 30-day mortality in ACS patients treated with clopidogrel (57). Prasugrel antiplatelet effect was also not significantly affected by concomitant administration of PPIs (58). In one study aspirin, was associated with increased risk of an adverse cardiovascular event (recurrent myocardial infarction, stroke, or cardiovascular death) when used concomitantly with PPIs possibly due to modification of intragastric pH which may reduce lipophilicity and bioavailability of aspirin (59). However, another study showed contradictory results: enhanced antiplatelet effects of enteric-coated aspirin in patients with ACS undergoing PCI (60). In this study methacrylic acid enteric-coated preparation of aspirin was used (60). Methacrylic acid is stable in acid solutions which allow the drug to pass intact through the upper gastrointestinal tract (60). However, gastric juice alkalinized by the addition of pantoprazole may cause earlier destabilization of the methacrylic acid sheath allowing aspirin to reach the duodenum already in its soluble form, thus assuring its rapid absorption (60). Concomitant use of clopidogrel and cimetidine, H₂-receptor antagonist which is a CYP2C19 inhibitor, was associated with increased risk of re-infarction in ACS patients in one study (28).

Non-steroidal anti-inflammatory drugs (NSAIDs) and antiplatelet drugs. Aspirin and ibuprofen share a common docking site in the cyclooxygenase-1 enzyme, so ibuprofen may competitively inhibit aspirin's antiplatelet effect (61). In one study there was a trend towards an increasing rate of recurrent acute myocardial infarction with longer duration of ibuprofen exposure, suggesting that regular, but not intermittent, use of ibuprofen may abrogate the benefits of aspirin in secondary prevention of acute myocardial infarction (61). In another study, among patients receiving antiplatelet therapy after myocardial infarction, the use of NSAIDs was associated with increased risk of excess thrombotic events, even after short-term treatment (62). Aspirin and ibuprofen did not adversely interact in a cohort of elderly patients discharged after myocardial infarction (63).

Clopidogrel and aprotinin. Findings of one study suggested that aprotinin may reduce antiplatelet effect of clopidogrel in ACS patients (64). Aprotinin increased ADP induced platelet aggregation from 84% to 94% corresponding to a median decrease in relative platelet inhibition of >50% (64). This effect was restricted to clopidogrel responders, suggesting that aprotinin interacts with clopidogrel-blocked ADP-receptors, making them available to ADP stimulation (64).

Clopidogrel and calcium channel blockers (CCBs). Some CCBs may inhibit CYP3A4 and may theoretically interfere with its metabolic conversion to active metabolite leading to the reduced clinical efficacy (65). However, results of the clinical studies have shown conflicting results. Some

studies involving ACS patients showed that CCBs did not interfere with the clopidogrel clinical efficacy (66, 67). One study showed that different guideline compliance of secondary prevention medications could modify this DDI: concomitant use of CCBs and clopidogrel was significantly associated with increased risk of ACS re-hospitalization in patients not compliant to guideline-recommended secondary prevention drugs (65).

Clopidogrel and statins. Both clopidogrel and some statins (e.g. simvastatin, atorvastatin, lovastatin) are metabolized via CYP3A4 (68). Studies involving ACS patients didn't show reduced clinical efficacy of clopidogrel when it was used concomitantly with statins (43, 66, 69-74).

Ticagrelor and antiepileptic CYP3A inducers. One study showed that co-administration of antiepileptic CYP3A enzyme pathway inducers (including phenytoin, carbamazepine and phenobarbital) may adversely affect the antiplatelet efficacy of ticagrelor as evident by higher P2Y₁₂ reaction units (PRU) values, representing suboptimal platelet inhibition in ACS patients (75). Over 1/3 of these patients developed high on-treatment reactivity, suggesting that they may be at risk for ischemic complications (75).

DDIs associated with decreased efficacy of thrombolytics

Nitroglycerin and recombinant tissue-type plasminogen activator (rTPA). Concurrent administration of nitroglycerin with rTPA (alteplase) in patients with acute myocardial infarction was associated with significantly reduced thrombolytic efficacy of rTPA: less frequent flow restoration (76, 77), longer time to reperfusion (76), greater incidence of in-hospital adverse events (76) and a higher incidence of coronary artery reocclusion (76). This DDI may be related to increase in hepatic blood flow in response to nitroglycerin resulting in increased catabolism of rTPA (76).

DDIs associated with decreased efficacy of anticoagulants

Nitroglycerin and heparin. Nitroglycerin induced qualitative antithrombin III abnormality may impair directly the ability of intravenous heparin to produce a state of systemic anticoagulation (78). However, evidence regarding interaction of these two drugs are conflicting as there are studies which suggest that intravenous nitroglycerin may induce heparin resistance and attenuate its anticoagulant effect in ACS patients (78, 79), while some studies did not confirm this finding (80, 81).

DDIs associated with increased risk of bleeding

Antiplatelet drugs, anticoagulants and thrombolytics and their combinations. Most DDIs associated with increased risk of bleeding involving anticoagulants, antiplatelet drugs and thrombolytics are pharmacodynamic. Dual antiplatelet therapy (e.g. aspirin + clopidogrel, aspirin + ticagrelor, aspirin + prasugrel) was associated with increased risk of



bleeding in ACS patients, including increased risk of major bleeding (82-87). Combination of an emerging antiplatelet drug vorapaxar (platelet thrombin receptor antagonist), and glycoprotein (GP) IIb/IIIa receptor inhibitors (88) was associated with increased bleeding risk in ACS patients. On the other hand, its combination with thienopyridines in some cases may lead to increased risk of clinically significant bleeding (89), while one study didn't observe significant interaction between clopidogrel and vorapaxar (90). Combining anticoagulants and antiplatelet drugs may also increase risk of bleeding in ACS patients (e.g. oral anticoagulants and aspirin or DAPT (91-95), thienopyridines and low molecular weight heparin (96), tirofiban and heparin (97)), as well as combinations of thrombolytics and antiplatelet drugs (particularly GP IIb/IIIa receptor inhibitors (98, 99)) or parenteral anticoagulants (99). Combination of thrombolytic (tenecteplase), parenteral anticoagulant (heparin) and DAPT (aspirin and clopidogrel) may also be associated with increased bleeding risk: orbital subperiosteal hematoma occurred in acute myocardial infarction patient on combination of these drugs (100).

Non-steroidal anti-inflammatory drugs (NSAIDs) and antithrombotic therapy. Among patients receiving antithrombotic therapy after myocardial infarction, the use of NSAIDs was associated with increased risk of bleeding (62). The association was observed for all antithrombotic treatment regimens (monotherapy with aspirin, clopidogrel, or a vitamin K antagonist; DAPT with aspirin plus clopidogrel, aspirin plus a vitamin K antagonist, or clopidogrel plus a vitamin K antagonist; or triple therapy including all three drugs) (62). There was no safe therapeutic window for concomitant NSAID use, because even short-term (0-3 days) treatment was associated with increased risk of bleeding (62). Also, one study reported occurrence of melena in a 68-year-old male patient with a history of chronic gastritis and myocardial infarction receiving clopidogrel and aspirin, who had also received a 4-day NSAID treatment for radiculitis and a 2-day parenteral methylprednisolone for drug-induced urticaria prior to hospitalization (101).

Selective serotonin reuptake inhibitors (SSRIs) and antiplatelet drugs. SSRIs use alone has been associated with an increased risk of bleeding (102). Platelets release serotonin at sites of bleeding and vascular damage, but they do not synthesize it and instead acquire it from the blood and store it, so SSRIs inhibition of serotonin transporters is thought to be the cause of increased bleeding risk (102). One study conducted in a large cohort of patients following acute myocardial infarction showed that patients taking a SSRI with aspirin or DAPT were at increased risk of bleeding (102).

Oral anticoagulants and drugs interfering with their metabolism. One case report described a 79-year-old patient on rivaroxaban for cardioembolic strokes and atrial fibrillation who was hospitalized for NSTEMI in the context of severe anemia related to gastrointestinal bleeding (103). It was hypothesized that both genetic and environmental factors contributed to increased susceptibility to rivaroxaban: the

homozygous presence of ABCB1 variant alleles (which encode P-glycoprotein) and reduced CYP3A4/5 activity due to DDI with simvastatin which could contributed to decreased rivaroxaban elimination (103). Another study reported increase in international normalized ratio after switching from atazanavir/ritonavir to darunavir/cobicistat in a HIV-infected 72-year-old patient on stable warfarin therapy with history of myocardial infarction (104). Removal of ritonavir in this patient led to the loss of CYP2C9 induction and subsequent increase in warfarin effect manifested by recurrent nosebleeds, which required a 60% reduction in warfarin dose (104).

Ticagrelor and cyclosporine. Co-administration of ticagrelor and cyclosporine may lead to increased exposure to both drugs, because both drugs are substrates and inhibitors of CYP3A4 and P-glycoprotein, as evidenced by two case reports (105, 106). In one case report a 49-year-old patient with a stable renal graft managed with cyclosporine with stable trough blood concentrations for several years was treated with ticagrelor for unstable angina pectoris (105). He complained of several minor bleeding events and his cyclosporine trough concentration increased 7 days after ticagrelor was started (105). The cyclosporine trough concentration in blood decreased within 13 days after ticagrelor was stopped and cyclosporine dose reduced (105). Patient did not have any bleeding events after ticagrelor was stopped, and switched to clopidogrel (105). In another case report a 58-year-old male patient who received cyclosporine for 5 years after renal transplantation developed gum bleeding and life-threatening bloody stool accompanied with the sudden drop of blood pressure 8 days after ticagrelor was added for treating ACS (106). This patient had decline in the hemoglobin level of 5.3 g/dL and received transfusion of 10 units of packed red blood cells (106).

Clopidogrel and ACE inhibitors. One study reported that in vitro coincubation of clopidogrel with ACE inhibitors increased clopidogrel bioactivation, as well as that concomitant treatment with these drugs in patients with first-time myocardial infarction was associated with increased risk of clinically important bleeding (107).

DDIs leading to rhabdomyolysis

Ticagrelor and statins. There are several case reports of rhabdomyolysis (108-112) associated with the concomitant use of ticagrelor and statins in patients who had ACS (three men (108, 111, 112) and two women (109, 110)). Age of the patients varied from 62 years (109) to 78 years (111). Statins involved in the interaction were: simvastatin (20 mg/day) (108), atorvastatin (80 mg/day in two cases (109, 110) and 40 mg/day in one case (112)) and rosuvastatin (40 mg/day) (111). Ticagrelor is metabolized through the enzymes CYP3A4/3A5 and is also a weak inhibitor of CYP3A, so it may increase the serum concentration of statins which are metabolized via CYP3A4 (e.g. simvastatin, atorvastatin) (108). Rosuvastatin is not metabolized by CYP3A4, however a deterioration of the renal function after introduction of ticagrelor led to the accumulation of rosuvastatin which



resulted in rhabdomyolysis (111). In one case amlodipine, a weak inhibitor of CYP3A4 (110), and in another clarithromycin, a potent CYP3A4 inhibitor (112), were also used concomitantly with atorvastatin and ticagrelor, so they may contributed to the increased exposure to these drugs (110, 112). One patient had normal kidney function at all times (108), acute kidney injury developed in three patients (109-111) and one patient had slightly increased urea and creatinine above reference values (112). Duration of concomitant therapy of statins and ticagrelor varied from one (111) to five months (108). All patients recovered from the rhabdomyolysis (108-112).

Fibrates and statins. Combined statin and fibrate therapy may also lead to rhabdomyolysis in patients with ACS (113, 114). Both statins and fibrates have been independently associated with a risk of muscle-related toxicity as monotherapy, and statin-fibrate combination therapy increases this risk further (113, 114). An 81-year-old male patient developed rhabdomyolysis without significant deterioration of renal function after seven days of concomitant use of pravastatin (20 mg/day) and fenofibrate (160 mg/day) (113). Treatment of rhabdomyolysis resulted in resolution of the skeletomuscular symptoms and clinical recovery (113). In another case report 63-year-old male patient developed rhabdomyolysis and acute renal failure after two weeks of combined use of lovastatin (20 mg twice daily) and gemfibrozil (600 mg twice daily) (114). Patient had to be on hemodialysis for 3 months until partial return of renal function occurred (creatinine clearance 22 mL/min) (114).

Statins metabolized via CYP3A4 and CYP3A4 inhibitors. Three-month combined use of simvastatin (80 mg/day) and diltiazem (240 mg/day), a CYP3A4 inhibitor, also resulted in rhabdomyolysis and renal failure in a 75-year-old man who had a history of previous myocardial infarction (115). Patient underwent hemodialysis and received intensive physiotherapy (115). Within three weeks, muscle pain disappeared, and he regained the functional ability of his legs, but he remained hemodialysis dependent (115).

DDIs associated with hepatotoxicity

Clopidogrel and atorvastatin. As previously mentioned, both clopidogrel and atorvastatin are metabolized via CYP3A4 (68). Two case reports described occurrence of hepatotoxicity when clopidogrel was used concomitantly with atorvastatin in ACS patients (68,116). Both patients were male, one was 58 years old (116) and other 61 years old (68). Dose of atorvastatin in the first patient was 20 mg/day (116) and in the second 10 mg/day (68) when hepatotoxicity occurred. One of the patients was also taking diltiazem and prednisone which both may affect CYP3A4 metabolism (116). After withdrawal of atorvastatin, ALT recovered to baseline level in 10 days, and then pravastatin was prescribed (116). Pravastatin, which does not undergo CYP metabolism, did not cause notable elevation of ALT during 2-month follow-up (116).

DDIs associated with adverse effects on cardiovascular system

Escitalopram and lansoprazole. QT interval prolongation and ventricular fibrillation developed in a 46-year-old patient with acute myocardial infarction probably due to enhanced QT interval prolonging effect of escitalopram caused by lansoprazole's inhibition of its metabolism via CYP2C19 (117).

Carvedilol and dobutamine. In a 68-year-old ACS patient 85-90 minutes after carvedilol administration (plasma peak time for carvedilol), blood pressure decreased up to 70/40 mmHg leading to severe hypotension when dobutamine was started and dobutamine dose increased (118). When dobutamine dose was decreased and dopamine started the patient's blood pressure increased (118).

Metoprolol and cocaine. One case report described a 54-year-old patient with a cocaine associated myocardial infarction who received metoprolol nearly two hours after presentation for persistent tachycardia (119). Shortly after, patient complained of crushing substernal chest pain, developed pulseless electrical activity, and could not be resuscitated (119). Beta blockers may exacerbate coronary vasoconstriction in patients on cocaine probably due to unopposed alpha adrenergic agonism which may lead to vasospasm followed by tissue ischemia and infarction (119).

Metoprolol and CYP2D6 inhibitors. Metoprolol is metabolized via CYP2D6 enzyme (120). A pronounced inhibition of metoprolol metabolism by paroxetine (CYP2D6 inhibitor) was observed in one study which included acute myocardial infarction patients, but without serious adverse effects (120). A reduction of metoprolol dose was required in two of 17 patients: one due to excessive bradycardia (<45 beats/min) and another due to severe orthostatic hypotension (120). Also, excessive hypotension (<100 mm Hg) was observed in four patients with initially low systolic blood pressure, but this could not be exclusively assigned to metoprolol action, but rather to combined medications (beta-blockers, mononitrates, ACE inhibitors) (120). Since this condition was well tolerated, a reduction of medication dosages was not required (120). Combination of oral terbinafine, another CYP2D6 inhibitor, and metoprolol also resulted in a clinically significant sinus bradycardia (37 beats/min) in a 63-year-old patient with a history of ACS (121). The heart rate ameliorated first with a decrease in the dose of metoprolol, which was subsequently changed to bisoprolol and the heart rate remained normal (121).

Amiodarone and antiviral drugs. A 53-year-old HIV positive patient with NSTEMI developed acquired long QT syndrome and torsades de pointes cardiac arrest in the context of combined use of amiodarone with antiretroviral agents (abacavir, lamivudine, darunavir and raltegravir) (122). Individually, amiodarone and antiretrovirals may increase QTc interval (122). Also, darunavir is CYP3A4 inhibitor so it may promote amiodarone toxicity via inhibition of its metabolism via CYP3A4 (122). In this patient QTc interval began to



normalize 5 days after discontinuation of amiodarone and antiretroviral agents. In another case report a 61-year-old patient with a history of ACS and hepatitis C virus infection on therapy with amiodarone and atenolol experienced multiple episodes of syncope, extreme bradycardia and cardiac asystole 30 minutes after first sofosbuvir and daclatasvir administration (123). Cardiopulmonary resuscitation and adrenalin restored sinus bradycardia (123). Subsequently, after discontinuation of amiodarone, sofosbuvir and daclatasvir cardiac evaluation was normal (123). Sofosbuvir, daclatasvir and amiodarone interact with P-glycoprotein and CYP3A4, but mechanism of these interactions is unknown (123). Factors that might have contributed to the observed events include concomitant therapy with a beta-blocker (123).

Mexiletine and theophylline. In a 55-year-old patient with a history of two acute myocardial infarctions a DDI between mexiletine and theophylline leading to ventricular arrhythmias on two occasions was reported (124). On the first occasion, mexiletine was added to a steady state theophylline regimen and resulted in a doubling of the theophylline level and an estimated half-life in excess of 12 hours suggesting that theophylline clearance was reduced by 30% to 50 % (124). Since arrhythmia was also noted at therapeutic theophylline concentrations, a pharmacodynamic drug interaction with additive effects, in addition to the pharmacokinetic interaction, may be postulated as both mexiletine and theophylline alone may induce arrhythmia (124).

ACE inhibitors and aspirin. Studies showed conflicting results regarding DDI involving these drugs. Aspirin blocks prostaglandin synthesis and ACE inhibitors tend to increase it, so there is a possibility for their antagonistic interaction (125). One study showed that aspirin antagonized the effect of enalapril on mortality after acute myocardial infarction suggesting that adding enalapril to patients on aspirin may be counteractive to survival (125). Several studies didn't show negative DDI between aspirin and lisinopril (126), captopril (127, 128) or ACE inhibitors in general when used in patients after myocardial infarction (129).

DDIs leading to serotonin syndrome

Escitalopram and methylene blue. One case report described a 62-year-old NSTEMI patient receiving chronic SSRI escitalopram who developed postcardiopulmonary bypass refractory vasoplegia (130). The vasoplegia was successfully treated with methylene blue, but the patient subsequently developed serotonin syndrome with abrupt onset of hyperthermia, upper extremity rigidity, encephalopathy, and cardiovascular instability (130). After discontinuation of all serotonergic medications, the patient slowly recovered with no apparent permanent complications (130). Methylene blue inhibits monoamine oxidase-A (the enzyme responsible for degrading serotonin, dopamine, and norepinephrine) and when given in combination with serotonergic medications it may lead to excess serotonin levels (130).

DDIs leading to drug-induced fever

Clonidine, duloxetine and atorvastatin. One report described a case of drug-induced fever probably associated with clonidine administration in which the higher dose of clonidine alone or in interaction with duloxetine and atorvastatin may have contributed to its development (131). A 66-year-old NSTEMI patient developed fever on the third day after the cardiac catheterization which ranged from 37.2°C to 38.9°C after dose of clonidine was increased to 0.2 mg per os three times a day to optimize blood pressure control (131). Diagnostic examinations did not reveal any source of infection (131). On the sixth day after admission, clonidine was reduced to the baseline dose of 0.1 mg per os three times a day and on the ninth day it was stopped (131). The patient was afebrile on the twelfth day (131). The mechanism by which clonidine might disrupt thermoregulation is still unclear, but both central and peripheral mechanisms may be implicated (131). Serotonergic, noradrenergic and dopaminergic neurotransmitter systems have been implicated in the mediation of drug-induced hyperthermia, so increase in these neurotransmitters may influence thermoregulatory system (131). It is possible that the interaction between the higher dose of clonidine and duloxetine (a serotonin-norepinephrine reuptake inhibitor), might have led to increased core temperature and drug-induced fever (131). Another contributing factor may have been concomitant administration of atorvastatin, CYP inhibitor, which might have inhibited metabolism of duloxetine (131).

DISCUSSION

This review has shown that ACS patients can be exposed to a variety of DDIs with diverse outcomes which include decreased efficacy of antiplatelet drugs, thrombolytics or anticoagulants, increased risk of bleeding, rhabdomyolysis, hepatotoxicity, adverse effects on cardiovascular system (e.g. QT interval prolongation, arrhythmias, excessive bradycardia, severe hypotension), serotonin syndrome and drug-induced fever. Majority of the DDIs involved antiplatelet drugs (e.g. aspirin, clopidogrel and ticagrelor). In addition, evidence of some of the reported DDIs is inconclusive as some of the studies have shown conflicting results (e.g. DDIs of clopidogrel and PPIs or CCBs; aspirin and ibuprofen, ACE inhibitors or PPIs; nitroglycerin and heparin).

DDIs leading to decreased efficacy of antiplatelet drugs have raised concern because of the possibility of increased risk of thrombotic events, but some of the studies evaluating these DDIs did not have consistent results (132). A prime example of such DDI is an interaction of clopidogrel and PPIs for which even several meta-analyses have shown conflicting results (133-135). Meta-analyses of randomized controlled trials endorsed the use of PPI with DAPT for reducing gastrointestinal bleeding without worsening cardiovascular outcomes, while meta-analyses of observational studies showed that PPI significantly increased the risk of all-cause mortality, cardiovascular mortality, myocardial infarction and stroke without reducing gastrointestinal bleeding and this difference was attributed to differences in design and limitations of each study type (133-135). The European Society of



Cardiology (ESC) currently recommends PPI use in combination with DAPT in all coronary artery disease patients as a measure to minimize bleeding risk, but with a note that omeprazole and esomeprazole would appear to have the highest propensity for clinically relevant DDIs, while pantoprazole and rabeprazole have the lowest (136). On the other hand, 2016 American College of Cardiology/American Heart Association (AHA) focused update recommends the concomitant use of PPI with DAPT in patients with a prior history or with a higher risk of gastrointestinal bleeding, but its routine use is not recommended in patients at low risk of gastrointestinal bleeding (137). H₂-receptor antagonists are often used as an alternative to PPIs, but this does not appear to be an adequate solution in all cases because they do not have the same efficacy as PPIs in reducing gastrointestinal events and may also act as competitive inhibitors of CYP2C19 (138). Also, there are no particular recommendations regarding clopidogrel and CCBs interaction (12). Regarding interaction of aspirin and ibuprofen, Food and Drug Administration issued a notice that the clinical implication of the interference by ibuprofen on the antiplatelet effect of aspirin is unclear, but that it is potentially important (139). It is stated that it is likely that risk is minimal with occasional use of ibuprofen and that patients who use immediate release aspirin (not enteric coated) and take a single dose of ibuprofen 400 mg should take it at least 30 minutes or longer after aspirin, or more than 8 hours before aspirin to avoid attenuation of aspirin's effect (139). Antiepileptic CYP3A inducers may adversely affect the antiplatelet efficacy of ticagrelor, so risks for DDI and mitigation of P2Y₁₂ inhibition must be weighed against discontinuation of the CYP3A inducer or switching to a thienopyridine (75).

A variety of studies reported that morphine may delay and attenuate exposure and action of oral P2Y₁₂ receptor inhibitors (clopidogrel, ticagrelor, prasugrel) in ACS patients (15-23). However, current guidelines still continue to recommend morphine as the drug of choice for pain relief in this setting, but with a warning that this DDI may lead to early treatment failure in susceptible individuals (6, 7). Recently published meta-analysis reported that the use of morphine for pain control in the setting of ACS was associated with an increased risk of in-hospital recurrent myocardial infarction and number needed to harm (NNH) was 125 (140). Although the value of NNH might be relatively high, it certainly raises important safety concerns considering high incidence of ACS and widespread use of morphine which translate into a considerable absolute number of events (140). This suggests a need for a cautious use of morphine in the ACS setting until further results of the adequately powered trials are available keeping in mind that the current guidelines recommendations regarding the use of morphine in ACS are mainly based on expert opinion rather than randomized clinical trials (140, 141).

Modern management of ACS includes a mix of antithrombotic therapy and invasive procedures which carry a risk of bleeding with a varying degree (142). DAPT reduces the risk of stent thrombosis, but its duration beyond one year

after PCI or myocardial infarction exerts majority of its benefits (136). Bleeding risk with DAPT is proportionally related to its duration, so the decision regarding DAPT duration should be dynamic and reassessed during the course of the initially selected DAPT regimen (136). In ACS patients regardless of the revascularization strategy, the default DAPT duration is 12 months, but 6-month therapy should be considered in high bleeding risk patients, while >12-month duration may be considered in patients who have tolerated DAPT without bleeding complications (136). Patients requiring oral anticoagulant in addition to DAPT should be considered at high risk of bleeding and the indication for oral anticoagulant should be reassessed and treatment continued only if there is a compelling indication (136). The duration of triple therapy should be limited to a maximum of 6 months or omitted after hospital discharge considering the ischemic and bleeding risk (136). In addition, patients may be at increased risk of bleeding due to DDIs with drugs used to treat other comorbidities (e.g. SSRIs, NSAIDs, corticosteroids and drugs which may interfere with metabolism of antithrombotic drugs), so clinicians should be cautious when prescribing new drugs to ACS patients. When bleeding occurs clinicians should weigh the risk related to ongoing bleeding, dose reduction, or temporary discontinuation of antithrombotic drugs, whenever possible, with rapid resumption of the initial antithrombotic therapy, depending on the possibility to treat bleeding and the half-life and reversibility of the effect of that drug (142). Discontinuation of antithrombotic therapy to minimize bleeding place the patient at increased risk of recurrent ischemia and infarction (142).

Concomitant use of statins and fibrates, ticagrelor or drugs which may inhibit metabolism of statins (e.g. diltiazem) may lead to the development of rhabdomyolysis in ACS patients as demonstrated by the several case reports included in this review (108-115). AHA published recommendations for management of clinically significant DDIs of statins (143). Regarding statin-fibrate interaction it is stated that fenofibrate (or fenofibric acid) is the preferred fibrate to use in combination with statins because of a reduced incidence of DDIs compared with statin-gemfibrozil combination therapy (143). However, even combination with fenofibrate was associated with the occurrence of rhabdomyolysis in ACS patients so caution is certainly needed even when fenofibrate is prescribed (113). Regarding ticagrelor-statin interaction some reviews point out that although a theoretical mechanism of this interaction exists, its clinical significance might be limited as ticagrelor is frequently used in ACS patients who simultaneously receive intensive, high-dose statin treatment which may itself lead to rhabdomyolysis (144). Regarding statin-ticagrelor DDIs, AHA stated that co-administration of ticagrelor and atorvastatin results in only a minor increase in statin systemic exposure and the combination is reasonable for appropriate patients (143). Also, combination therapy with ticagrelor and lovastatin or simvastatin may be considered and in this case dose of simvastatin and lovastatin should not exceed 40 mg daily (143). However, as demonstrated by one of the reported cases the combination of ticagrelor with simvastatin may pose a risk for rhabdomyolysis



even with low-dose simvastatin (20 mg/day), so caution is certainly necessary, especially in older populations (108). As ticagrelor-statin interaction might be amplified by co-administration of drugs that are strong or moderate inhibitors of CYP3A close monitoring and dose alteration are also recommended when multiple CYP3A inhibitors are administered with statins metabolized via this pathway (110). In general, close clinical monitoring, particularly in old patients with impaired renal function or when high doses of statins are prescribed with interacting drugs is certainly needed (115).

Patients with ACS may be at particular risk to experience adverse effects on cardiovascular system due to DDIs with possible outcomes including QT interval prolongation, arrhythmias, excessive bradycardia and severe hypotension. So, there is a need for close monitoring of electrocardiogram, QT interval, serum electrolytes and blood pressure in patients receiving a combination of drugs which may expose patients to these adverse effects (122). Negative interaction of ACE inhibitors and aspirin is highly debatable, despite some meta-analyses suggesting an antagonistic interaction between them, but with results not strong enough to contraindicate the aspirin-ACE inhibitor association or to prove clinical relevance of this interaction (145-147). Current ESC guidelines recommend ACE inhibitor use in ACS patients, particularly in those with systolic left ventricular dysfunction or heart failure, hypertension or diabetes (6, 7). Consequences of some of the DDIs may include hepatotoxicity, particularly associated with statin treatment, so it is important to carefully monitor liver function tests in ACS patients, especially if drugs which may inhibit their metabolism are used concomitantly (116). Also, some unexpected consequences may occur as a result of DDIs, such as high fever, so clinicians should be vigilant and keep in mind that some of the adverse outcomes observed in patients may be due to DDIs. In the end, it should be noted that this review summarized DDIs evaluated or reported in ACS patients, so some of the clinically relevant DDIs of drugs that may be used for treatment of ACS or other patient's comorbidities evaluated in other populations could have been omitted. Clinicians who prescribe drugs to ACS patients should always check their prescriptions for potential DDIs and explore their clinical relevance.

CONCLUSION

ACS patients may be exposed to a variety of DDIs with diverse outcomes which include decreased efficacy of antiplatelet drugs, thrombolytics or anticoagulants, increased risk of bleeding, rhabdomyolysis, hepatotoxicity, adverse effects on cardiovascular system (e.g. QT interval prolongation, arrhythmias, excessive bradycardia, severe hypotension), serotonin syndrome and drug-induced fever. Majority of the DDIs involved antiplatelet drugs (e.g. aspirin, clopidogrel and ticagrelor). Evidence of some of the reported DDIs is inconclusive as some of the studies have shown conflicting results. It is essential to evaluate DDIs in the population of patients in which drug is intended to be used, emphasizing the need for additional post-marketing and population-

based studies to evaluate the true effects of disease states and other factors on the clinical outcomes of DDIs. Clinicians should be attentive to the potential for DDIs and their associated harm in order to minimize or, if possible, avoid medication-related adverse events in ACS patients.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Kumar A, Cannon CP. Acute Coronary Syndromes: Diagnosis and Management, Part I. *Mayo Clin Proc* 2009; 84(10): 917-38.
2. Boden H, van der Hoeven BL, Karalis I, Schalij MJ, Jukema JW. Management of acute coronary syndrome: achievements and goals still to pursue. Novel developments in diagnosis and treatment. *J Intern Med* 2012; 271(6): 521-36.
3. Patel NK, Elmariah S. Acute Coronary Syndromes. In: Lau JF, Barnes GD, Streiff MB, editors. *Anticoagulation Therapy*. Cham: Springer International Publishing; 2018. p. 197-216.
4. Dhoble A, Anderson HV. Strategies in Acute Coronary Syndrome. In: Lanzer P, editor. *Textbook of Catheter-Based Cardiovascular Interventions*. Cham: Springer International Publishing; 2018. p. 921-38.
5. Bassand JP. Drug interactions in the setting of acute coronary syndromes and dual anti-platelet therapy. *Eur Heart J Suppl* 2006; 8(suppl G): G35-7.
6. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; 37(3): 267-315.
7. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2018; 39: 119-77.
8. Scheife RT, Hines LE, Boyce RD, Chung SP, Momper JD, Sommer CD, et al. Consensus recommendations for systematic evaluation of drug-drug interaction evidence for clinical decision support. *Drug Saf* 2015; 38(2): 197-206.



9. Baxter K. (2010). *Stockley's Drug Interactions* (9th ed.). London: Pharmaceutical Press.
10. de Lima TAM, de Godoy MF. Drug-drug interactions in prescriptions for hospitalized elderly with Acute Coronary Syndrome. *Rev Eletrônica Enferm* 2017; 19: a24.
11. Pejčić AV, Janković SM, Davidović G. Drug-drug interactions in patients with acute coronary syndrome across phases of treatment. *Intern Emerg Med* 2019; 14(3): 411–22.
12. Dunn SP, Holmes DR, Moliterno DJ. Drug-drug interactions in cardiovascular catheterizations and interventions. *JACC Cardiovasc Interv* 2012; 5(12): 1195–208.
13. Snyder BD, Polasek TM, Doogue MP. Drug interactions: principles and practice. *Aust Prescr* 2012; 35: 85–8.
14. Cecchi E. Drug-drug interaction knowledge to save the patient from iatrogenic disease and to improve the diagnostic process. *Intern Emerg Med* 2019; 14(3): 345–7.
15. Zeymer U, Mark B, Montalescot G, Thiele H, Zahn R. Influence of morphine on the effect of clopidogrel and prasugrel in patients with ST elevation myocardial infarction. Results of the ETAMI trial. *Eur Heart J* 2015; 36(Abstract Supplement): 227–8.
16. Parodi G, Bellandi B, Xanthopoulou I, Capranzano P, Capodanno D, Valenti R, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. *Circ Cardiovasc Interv* 2015; 8(1): e001593.
17. Bellandi B, Zocchi C, Xanthopoulou I, Scudiero F, Valenti R, Migliorini A, et al. Morphine use and myocardial reperfusion in patients with acute myocardial infarction treated with primary PCI. *Int J Cardiol* 2016; 221: 567–71.
18. Thomas MR, Morton AC, Hossain R, Chen B, Luo L, Shahari NN, et al. Morphine delays the onset of action of prasugrel in patients with prior history of ST-elevation myocardial infarction. *Thromb Haemost* 2016; 116(1): 96–102.
19. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, et al. Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial. *Eur Heart J* 2016; 37(3): 245–52.
20. Franchi F, Rollini F, Cho JR, Bhatti M, DeGroat C, Ferrante E, et al. Impact of Escalating Loading Dose Regimens of Ticagrelor in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention: Results of a Prospective Randomized Pharmacokinetic and Pharmacodynamic Investigation. *JACC Cardiovasc Interv* 2015; 8(11): 1457–67.
21. Silvain J, Storey RF, Cayla G, Esteve J-B, Dillinger J-G, Rousseau H, et al. P2Y₁₂ receptor inhibition and effect of morphine in patients undergoing primary PCI for ST-segment elevation myocardial infarction. The PRIVATE-ATLANTIC study. *Thromb Haemost* 2016; 116(2): 369–78.
22. Lapostolle F, van't Hof AW, Hamm CW, Stibbe O, Ecollan P, Collet J-P, et al. Morphine and Ticagrelor Interaction in Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction: ATLANTIC-Morphine. *Am J Cardiovasc Drugs* 2019; 19(2): 173–83.
23. Farag M, Spinhakis N, Srinivasan M, Sullivan K, Wellsted D, Gorog DA. Morphine Analgesia Pre-PPCI Is Associated with Prothrombotic State, Reduced Spontaneous Reperfusion and Greater Infarct Size. *Thromb Haemost* 2018; 118(3): 601–12.
24. Bhurke SM, Martin BC, Li C, Franks AM, Bursac Z, Said Q. Effect of the clopidogrel-proton pump inhibitor drug interaction on adverse cardiovascular events in patients with acute coronary syndrome. *Pharmacotherapy* 2012; 32(9): 809–18.
25. Ortolani P, Marino M, Marzocchi A, De Palma R, Branzi A. One-year clinical outcome in patients with acute coronary syndrome treated with concomitant use of clopidogrel and proton pump inhibitors: results from a regional cohort study. *J Cardiovasc Med (Hagerstown)* 2012; 13(12): 783–9.
26. Valkhoff VE, 't Jong GW, Van Soest EM, Kuipers EJ, Sturkenboom MC. Risk of recurrent myocardial infarction with the concomitant use of clopidogrel and proton pump inhibitors. *Aliment Pharmacol Ther* 2011; 33(1): 77–88.
27. Tsai YW, Wen YW, Huang WF, Chen PF, Kuo KN, Hsiao FY. Cardiovascular and gastrointestinal events of three antiplatelet therapies: clopidogrel, clopidogrel plus proton-pump inhibitors, and aspirin plus proton-pump inhibitors in patients with previous gastrointestinal bleeding. *J Gastroenterol* 2011; 46(1): 39–45.
28. Sheng-Wen Wang S, Tsai SS, Hsu PC, Yang CY, Wu DC. Concomitant use of clopidogrel and proton pump inhibitors or cimetidine after acute myocardial infarction would increase the risk of re-infarction. *Am J Gastroenterol* 2009; 104(12): 3116–7.
29. Rassen JA, Choudhry NK, Avorn J, Schneeweiss S. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome. *Circulation* 2009; 120(23): 2322–9.
30. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; 301(9): 937–44.
31. Depta JP, Lenzini PA, Lanfear DE, Wang TY, Spertus JA, Bach RG, et al. Clinical outcomes associated with proton pump inhibitor use among clopidogrel-treated patients within CYP2C19 genotype groups following acute myocardial infarction. *Pharmacogenomics J* 2015; 15(1): 20–5.
32. Evanchan J, Donnally MR, Binkley P, Mazzaferri E. Recurrence of Acute Myocardial Infarction in Patients Discharged on Clopidogrel and a Proton Pump Inhibitor After Stent Placement for Acute Myocardial Infarction. *Clin Cardiol* 2010; 33(3): 168–71.



33. Goodman SG, Clare R, Pieper KS, Nicolau JC, Storey RF, Cantor WJ, et al. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes trial. *Circulation* 2012; 125(8): 978–86.
34. Jackson LR, Peterson ED, McCoy LA, Ju C, Zettler M, Baker BA, et al. Impact of Proton Pump Inhibitor Use on the Comparative Effectiveness and Safety of Prasugrel Versus Clopidogrel: Insights From the Treatment With Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) Study. *J Am Heart Assoc* 2016;5(10).
35. Zou JJ, Chen SL, Tan J, Lin L, Zhao YY, Xu HM, et al. Increased Risk for Developing Major Adverse Cardiovascular Events in Stented Chinese Patients Treated with Dual Antiplatelet Therapy after Concomitant Use of the Proton Pump Inhibitor. *PLOS ONE* 2014; 9(1): e84985.
36. Parri MS, Gianetti J, Dushpanova A, Della Pina F, Saracini C, Marcucci R, et al. Pantoprazole significantly interferes with antiplatelet effect of clopidogrel: results of a pilot randomized trial. *Int J Cardiol* 2013; 167(5): 2177–81.
37. Fernando H, Bassler N, Habersberger J, Sheffield LJ, Sharma R, Dart AM, et al. Randomized double-blind placebo-controlled crossover study to determine the effects of esomeprazole on inhibition of platelet function by clopidogrel. *J Thromb Haemost* 2011; 9(8): 1582–9.
38. Chyrchel B, Surdacki A, Chyrchel M, Dudek D, Dubiel JS. Separate dosing of clopidogrel and omeprazole may improve platelet inhibition on dual antiplatelet therapy. *Int J Cardiol* 2011; 149(1): 124–5.
39. Fontes-Carvalho R, Albuquerque A, Araújo C, Pimentel-Nunes P, Ribeiro VG. Omeprazole, but not pantoprazole, reduces the antiplatelet effect of clopidogrel: a randomized clinical crossover trial in patients after myocardial infarction evaluating the clopidogrel–PPIs drug interaction. *Eur J Gastroenterol Hepatol* 2011; 23(5): 396–404.
40. Ren Y, Zhao M, Chen Y, Chen L, Liu H, Wang Y, et al. Omeprazole affects clopidogrel efficacy but not ischemic events in patients with acute coronary syndrome undergoing elective percutaneous coronary intervention. *Chin Med J (Engl)* 2011; 124(6): 856–61.
41. Tsukahara K, Kimura K, Morita S, Ebina T, Kosuge M, Hibi K, et al. Impact of concomitant use of proton-pump inhibitors and thienopyridine derivatives on the antiplatelet effects. *J Cardiol* 2011; 57(3): 275–82.
42. Cuisset T, Frere C, Quilici J, Poyet R, Gaborit B, Bali L, et al. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose the PACA (Proton Pump Inhibitors And Clopidogrel Association) prospective randomized study. *J Am Coll Cardiol* 2009; 54(13): 1149–53.
43. Zhang J, Wang D, Du J, Qu G, Du J, Deng S, et al. Efficacy of Clopidogrel and Clinical Outcome When Clopidogrel Is Coadministered With Atorvastatin and Lansoprazole: A Prospective, Randomized, Controlled Trial. *Medicine (Baltimore)* 2015; 94(50): e2262.
44. Liu LP, Wang Y, Si R, Yuan M, Cheng K, Guo WY. Esomeprazole and rabeprazole did not reduce antiplatelet effects of aspirin/clopidogrel dual therapy in patients undergoing percutaneous coronary intervention: a prospective, randomized, case–control study. *Expert Opin Pharmacother* 2016; 17(1): 7–16.
45. Lu F, Tong Z, Mao Y, Wu D, Xu J. [Impact of proton pump inhibitor omeprazole on the antiplatelet effect of clopidogrel in individuals with various CYP2C19*2 genotypes]. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2012; 29(4): 478–81.
46. Yano H, Tsukahara K, Morita S, Endo T, Sugano T, Hibi K, et al. Influence of omeprazole and famotidine on the antiplatelet effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes: a prospective, randomized, multicenter study. *Circ J* 2012; 76(11): 2673–80.
47. Bolek T, Samoř M, Šimonová R, Kovář F, Fedor M, Galajda P, et al. Does Pantoprazole Affect the On-Treatment Platelet Reactivity in Patients With Acute STEMI Treated With ADP Receptor Blockers?—A Pilot Prospective Study. *Am J Ther* 2017; 24(2): e162–6.
48. Lin CF, Shen LJ, Wu FL, Bai CH, Gau CS. Cardiovascular outcomes associated with concomitant use of clopidogrel and proton pump inhibitors in patients with acute coronary syndrome in Taiwan. *Br J Clin Pharmacol* 2012; 74(5): 824–34.
49. Macaione F, Montaina C, Evola S, Novo G, Novo S. Impact of dual antiplatelet therapy with proton pump inhibitors on the outcome of patients with acute coronary syndrome undergoing drug-eluting stent implantation. *ISRN Cardiol* 2012; 2012: 692761.
50. Chitose T, Hokimoto S, Oshima S, Nakao K, Fujimoto K, Miyao Y, et al. Clinical outcomes following coronary stenting in Japanese patients treated with and without proton pump inhibitor. *Circ J* 2012; 76(1): 71–8.
51. Hsiao FY, Mullins CD, Wen YW, Huang WF, Chen PF, Tsai YW. Relationship between cardiovascular outcomes and proton pump inhibitor use in patients receiving dual antiplatelet therapy after acute coronary syndrome. *Pharmacoepidemiol Drug Saf* 2011; 20(10): 1043–9.
52. Douglas IJ, Evans SJW, Hingorani AD, Grosso AM, Timmis A, Hemingway H, et al. Clopidogrel and interaction with proton pump inhibitors: comparison between cohort and within person study designs. *BMJ* 2012; 345: e4388.
53. Simon T, Steg PG, Gilard M, Blanchard D, Bonello L, Hanssen M, et al. Clinical events as a function of proton pump inhibitor use, clopidogrel use, and cytochrome P450 2C19 genotype in a large nationwide cohort of acute myocardial infarction: results from the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) registry. *Circulation* 2011; 123(5): 474–82.
54. Gaspar A, Ribeiro S, Nabais S, Rocha S, Azevedo P, Pereira MA, et al. Proton pump inhibitors in patients



- treated with aspirin and clopidogrel after acute coronary syndrome. *Rev Port Cardiol* 2010; 29(10): 1511–20.
55. Amariles P, Holguín H, Angulo NY, Betancourth PM, Ceballos M. [Effect of drug interaction between clopidogrel and omeprazole in hospital readmission of patients by a recurrent acute coronary syndrome: a case-control study]. *Aten Primaria* 2014; 46(8): 426–32.
 56. Gao QP, Sun Y, Sun YX, Wang LF, Fu L. Early use of omeprazole benefits patients with acute myocardial infarction. *J Thromb Thrombolysis* 2009; 28(3): 282–7.
 57. Wu H, Jing Q, Wang J, Guo X. Pantoprazole for the prevention of gastrointestinal bleeding in high-risk patients with acute coronary syndromes. *J Crit Care* 2011; 26(4): 434.e1–6.
 58. Aradi D, Kuliczowski W, Atar D, Serebruany VL. Inter-patient variability and impact of proton pump inhibitors on platelet reactivity after prasugrel. *Thromb Haemost* 2012; 107(2): 338–45.
 59. Charlot M, Grove EL, Hansen PR, Olesen JB, Ahlehoff O, Selmer C, et al. Proton pump inhibitor use and risk of adverse cardiovascular events in aspirin treated patients with first time myocardial infarction: nationwide propensity score matched study. *BMJ* 2011; 342: d2690.
 60. Kasprzak M, Koziński M, Bielis L, Boinska J, Plazuk W, Marciniak A, et al. Pantoprazole may enhance antiplatelet effect of enteric-coated aspirin in patients with acute coronary syndrome. *Cardiol J* 2009; 16(6): 535–44.
 61. Hudson M, Baron M, Rahme E, Pilote L. Ibuprofen may abrogate the benefits of aspirin when used for secondary prevention of myocardial infarction. *J Rheumatol* 2005; 32(8): 1589–93.
 62. Schjerning Olsen AM, Gislason GH, McGettigan P, Fosbøl E, Sørensen R, Hansen ML, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. *JAMA* 2015; 313(8): 805–14.
 63. Curtis JP, Wang Y, Portnay EL, Masoudi FA, Havranek EP, Krumholz HM. Aspirin, ibuprofen, and mortality after myocardial infarction: retrospective cohort study. *BMJ* 2003; 327(7427): 1322–3.
 64. Lindvall G, Sartipy U, Bjessmo S, Svenarud P, Lindvall B, van der Linden J. Aprotinin reduces the antiplatelet effect of clopidogrel. *Interact Cardiovasc Thorac Surg* 2009; 9(2): 178–81.
 65. Wang CY, Lin ZF, Lee CM, Tsai YW, Huang TY, Shen LJ, et al. Concomitant use of calcium channel blockers with dual antiplatelet therapy and re-hospitalization for acute coronary syndrome. *Pharmacoepidemiol Drug Saf* 2017; 26(3): 229–38.
 66. Ojeifo O, Wiviott SD, Antman EM, Murphy SA, Udell JA, Bates ER, et al. Concomitant administration of clopidogrel with statins or calcium-channel blockers: insights from the TRITON-TIMI 38 (trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38). *JACC Cardiovasc Interv* 2013; 6(12): 1275–81.
 67. Olesen JB, Gislason GH, Charlot MG, Fosbøl EL, Andersen C, Weeke P, et al. Calcium-channel blockers do not alter the clinical efficacy of clopidogrel after myocardial infarction: a nationwide cohort study. *J Am Coll Cardiol* 2011; 57(4): 409–17.
 68. Thotakura S, Singh A, Khera K, Chauhan S, Devasia T. Atorvastatin-induced hepatotoxicity, increased by clopidogrel stress on CYP450 Enzyme: Understanding the mechanism through a case. *J Appl Pharm Sci* 2018; 8(4): 168–170.
 69. Mitsios JV, Papathanasiou AI, Rodis FI, Elisaf M, Goudevenos JA, Tselepis AD. Atorvastatin Does Not Affect the Antiplatelet Potency of Clopidogrel When It Is Administered Concomitantly for 5 Weeks in Patients With Acute Coronary Syndromes. *Circulation*. 2004; 109(11): 1335–8.
 70. Lotfi A, Schweiger MJ, Giugliano GR, Murphy SA, Cannon CP, TIMI 22 Investigators. High-dose atorvastatin does not negatively influence clinical outcomes among clopidogrel treated acute coronary syndrome patients—a Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) analysis. *Am Heart J* 2008; 155(5): 954–8.
 71. Lim MJ, Spencer FA, Gore JM, Dabbous OH, Agnelli G, Kline-Rogers EM, et al. Impact of combined pharmacologic treatment with clopidogrel and a statin on outcomes of patients with non-ST-segment elevation acute coronary syndromes: perspectives from a large multinational registry. *Eur Heart J* 2005; 26(11): 1063–9.
 72. Han Y, Li C, Li Y, Kang J, Yan C. [The antiplatelet effect of clopidogrel is not attenuated by statin treatment in patients with acute coronary syndromes undergone coronary stenting]. *Zhonghua Xin Xue Guan Bing Za Zhi* 2007; 35(9): 788–92.
 73. Mukherjee D, Kline-Rogers E, Fang J, Munir K, Eagle KA. Lack of clopidogrel-CYP3A4 statin interaction in patients with acute coronary syndrome. *Heart Br Card Soc* 2005; 91(1): 23–6.
 74. Wienbergen H, Gitt AK, Schiele R, Juenger C, Heer T, Meisenzahl C, et al. Comparison of clinical benefits of clopidogrel therapy in patients with acute coronary syndromes taking atorvastatin versus other statin therapies. *Am J Cardiol* 2003; 92(3): 285–8.
 75. Pourdjabbar A, Hibbert B, Chong AY, Abunassar J, Malhotra N, Whitten TA, et al. A pharmacodynamic analysis for the co-administration of inducers of CYP3A with ticagrelor: A cautionary tale in managing patients with acute coronary syndromes. *Int J Cardiol* 2016; 214: 423–5.
 76. Romeo F, Rosano GM, Martuscelli E, De Luca F, Bianco C, Colistra C, et al. Concurrent nitroglycerin administration reduces the efficacy of recombinant tissue-type plasminogen activator in patients with acute anterior wall myocardial infarction. *Am Heart J* 1995; 130(4): 692–7.
 77. Nicolini FA, Ferrini D, Ottani F, Galvani M, Ronchi A, Behrens PH, et al. Concurrent nitroglycerin therapy impairs tissue-type plasminogen activator-induced thrombolysis in patients with acute myocardial infarction. *Am J Cardiol* 1994; 74(7): 662–6.



78. Becker RC, Corrao JM, Bovill EG, Gore JM, Baker SP, Miller ML, et al. Intravenous nitroglycerin-induced heparin resistance: a qualitative antithrombin III abnormality. *Am Heart J* 1990; 119(6): 1254–61.
79. Habbab MA, Haft JI. Heparin resistance induced by intravenous nitroglycerin. A word of caution when both drugs are used concomitantly. *Arch Intern Med* 1987; 147(5): 857–60.
80. Gonzalez ER, Jones HD, Graham S, Elswick RK. Assessment of the drug interaction between intravenous nitroglycerin and heparin. *Ann Pharmacother* 1992; 26(12): 1512–4.
81. Nottestad SY, Mascette AM. Nitroglycerin-induced heparin resistance: absence of interaction at clinically relevant doses. *Mil Med* 1994; 159(8): 569–71.
82. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345(7): 494–502.
83. Gille J, Bernotat J, Böhm S, Behrens P, Löhr JF. Spontaneous hemarthrosis of the knee associated with clopidogrel and aspirin treatment. *Z Rheumatol* 2003; 62(1): 80–1.
84. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. *Circulation* 2004; 110(10): 1202–8.
85. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015; 372(19): 1791–800.
86. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; 357(20): 2001–15.
87. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361(11): 1045–57.
88. Cornel JH, Tricoci P, Lokhnygina Y, Moliterno DJ, Wallentin L, Armstrong PW, et al. Glycoprotein IIb/IIIa Receptor Inhibitors in Combination With Vorapaxar, a Platelet Thrombin Receptor Antagonist, Among Patients With Non-ST-Segment Elevation Acute Coronary Syndromes (from the TRACER Trial). *Am J Cardiol* 2015; 115(10): 1325–32.
89. Bohula EA, Aylward PE, Bonaca MP, Corbalan RL, Kiss RG, Murphy SA, et al. Efficacy and Safety of Vorapaxar With and Without a Thienopyridine for Secondary Prevention in Patients With Previous Myocardial Infarction and No History of Stroke or Transient Ischemic Attack: Results from TRA 2°P-TIMI 50. *Circulation* 2015; 132(20): 1871–9.
90. Tricoci P, Lokhnygina Y, Huang Z, Van de Werf F, Cornel JH, Chen E, et al. Vorapaxar with or without clopidogrel after non-ST-segment elevation acute coronary syndromes: results from the thrombin receptor antagonist for clinical event reduction in acute coronary syndrome trial. *Am Heart J* 2014; 168(6): 869–77.e1.
91. Hess CN, James S, Lopes RD, Wojdyla DM, Neely ML, Liaw D, et al. Apixaban Plus Mono Versus Dual Antiplatelet Therapy in Acute Coronary Syndromes: Insights From the APPRAISE-2 Trial. *J Am Coll Cardiol* 2015; 66(7): 777–87.
92. Effects of long-term, moderate-intensity oral anticoagulation in addition to aspirin in unstable angina. The Organization to Assess Strategies for Ischemic Syndromes (OASIS) Investigators. *J Am Coll Cardiol* 2001; 37(2): 475–84.
93. Sámóczy M, Farkas A, Sipos E, Tarján J. [Adverse effects of combined use of acenocoumarol and acetylsalicylic acid after myocardial infarction and unstable angina]. *Orv Hetil* 1995; 136(4): 177–9.
94. Buresly K, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med*. 2005; 165(7): 784–9.
95. Sørensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jørgensen C, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009; 374(9706): 1967–74.
96. Stiles MK, Dabbous OH, Fox KAA, GRACE investigators. Bleeding events with antithrombotic therapy in patients with unstable angina or non-ST-segment elevation myocardial infarction; insights from a large clinical practice registry (GRACE). *Heart Lung Circ* 2008; 17(1): 5–8.
97. Kim JH, Jeong MH, Rhew JY, Lim JH, Yun KH, Kim KH, et al. Long-Term Clinical Outcomes of Platelet Glycoprotein IIb/IIIa Inhibitor Combined With Low Molecular Weight Heparin in Patients With Acute Coronary Syndrome. *Circ J* 2005; 69(2): 159–64.
98. Savonitto S, Armstrong PW, Lincoff AM, Jia G, Sila CA, Booth J, et al. Risk of intracranial haemorrhage with combined fibrinolytic and glycoprotein IIb/IIIa inhibitor therapy in acute myocardial infarction: Dichotomous response as a function of age in the GUSTO V trial. *Eur Heart J* 2003; 24(20): 1807–14.
99. Sinnaeve PR, Huang Y, Bogaerts K, Vahanian A, Adgey J, Armstrong PW, et al. Age, outcomes, and treatment effects of fibrinolytic and antithrombotic combinations: Findings from Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT)-3 and ASSENT-3 PLUS. *Am Heart J* 2006; 152(4): 684.e1–9.
100. Amisshah-Arthur KN, Groppe M, Scotcher S. Orbital subperiosteal hematoma after thrombolysis and anticoagulation for acute myocardial infarction. *J Neuroophthalmol* 2009; 29(3): 250–1.



101. Ganeva M, Gancheva T, Baldaranov I, Troeva J, Hristakieva E. Screening for adverse drug interactions in dermatology patients. *Trakia J Sci* 2010; 8(2): 266–71.
102. Labos C, Dasgupta K, Nedjar H, Turecki G, Rahme E. Risk of bleeding associated with combined use of selective serotonin reuptake inhibitors and antiplatelet therapy following acute myocardial infarction. *CMAJ* 2011; 183(16): 1835–43.
103. Ing Lorenzini K, Daali Y, Fontana P, Desmeules J, Samer C. Rivaroxaban-Induced Hemorrhage Associated with ABCB1 Genetic Defect. *Front Pharmacol* 2016; 7: 494.
104. Tseng AL, Luetkehoelter J, Walmsley SL. Increase in international normalized ratio after switching from atazanavir/ritonavir to darunavir/cobicistat in a patient on warfarin: boosters are not always equal. *AIDS* 2017; 31(1): 175–6.
105. van Sloten TT, de Klaver PAG, van den Wall Bake AWL. Co-administration of cyclosporine and ticagrelor may lead to a higher exposure to cyclosporine: a case report of a 49-year-old man. *Br J Clin Pharmacol* 2018; 84(1): 208–10.
106. Zhang C, Shen L, Cui M, Liu X, Gu Z. Ticagrelor-induced life-threatening bleeding via the cyclosporine-mediated drug interaction: A case report. *Medicine (Baltimore)* 2017; 96(37): e8065.
107. Kristensen KE, Zhu HJ, Wang X, Gislason GH, Torp-Pedersen C, Rasmussen HB, et al. Clopidogrel Bioactivation and Risk of Bleeding in Patients Cotreated With Angiotensin-Converting Enzyme Inhibitors After Myocardial Infarction: A Proof-of-Concept Study. *Clin Pharmacol Ther* 2014; 96(6): 713–22.
108. Mroczek SM, Rassaf T, Totzeck M. Ticagrelor Leads to Statin-Induced Rhabdomyolysis: A Case Report. *Am J Case Rep* 2017; 18: 1238–41.
109. Kido K, Wheeler MB, Seratnahaei A, Bailey A, Bain JA. Rhabdomyolysis precipitated by possible interaction of ticagrelor with high-dose atorvastatin. *J Am Pharm Assoc* 2015; 55(3): 320–3.
110. Banakh I, Haji K, Kung R, Gupta S, Tiruvoipati R. Severe Rhabdomyolysis due to Presumed Drug Interactions between Atorvastatin with Amlodipine and Ticagrelor. *Case Rep Crit Care* 2017; 2017: 3801819.
111. van Vuren AJ, de Jong B, Bootsma HPR, Van der Veen MJ, Feith GW. Ticagrelor-induced renal failure leading to statin-induced rhabdomyolysis. *Neth J Med.* 2015; 73(3): 136–8.
112. Cenjor Martín R, Gutiérrez-Madrid E, Martín-Sánchez FJ, Cuervo Pinto R. [Iatrogenic rhabdomyolysis in a patient with ischemic heart disease]. *Med Clin (Barc).* 2016; 146(10): e57–8.
113. Jozic T, Terzic B, Mitrovic P, Kostic J, Milanov M, Stojanovic M, et al. Combined statin-fibrate therapy-induced rhabdomyolysis: Case report. *Hospital Pharmacology - International Multidisciplinary Journal* 2014; 1(1): 22–6.
114. Marais GE, Larson KK. Rhabdomyolysis and acute renal failure induced by combination lovastatin and gemfibrozil therapy. *Ann Intern Med* 1990; 112(3): 228–30.
115. Peces R, Pobes A. Rhabdomyolysis associated with concurrent use of simvastatin and diltiazem. *Nephron* 2001; 89(1): 117–8.
116. Liu Y, Cheng Z, Ding L, Fang F, Cheng KA, Fang Q, et al. Atorvastatin-induced acute elevation of hepatic enzymes and the absence of cross-toxicity of pravastatin. *Int J Clin Pharmacol Ther* 2010; 48(12): 798–802.
117. Tada T, Nakata J, Sugawara H, Nishizawa K, Sunaga D, Sato K, et al. [Case report; Selective serotonin reuptake inhibitor induced QT prolongation and ventricular fibrillation in acute myocardial infarction]. *Nihon Naika Gakkai Zasshi* 2014; 103(3): 738–40.
118. Vural M. [Role of the drug interaction between carvedilol and dobutamine in inducing of severe hypotension in a case with acute coronary syndrome]. *Anadolu Kardiyol Derg* 2007; 7(2): 229.
119. Fareed FN, Chan G, Hoffman RS. Death temporally related to the use of a Beta adrenergic receptor antagonist in cocaine associated myocardial infarction. *J Med Toxicol* 2007; 3(4): 169–72.
120. Goryachkina K, Burbello A, Boldueva S, Babak S, Bergman U, Bertilsson L. Inhibition of metoprolol metabolism and potentiation of its effects by paroxetine in routinely treated patients with acute myocardial infarction (AMI). *Eur J Clin Pharmacol* 2008; 64(3): 275–82.
121. Bebawi E, Jouni SS, Tessier A-A, Frenette AJ, Brindamour D, Doré M. A metoprolol-terbinafine combination induced bradycardia. *Eur J Drug Metab Pharmacokinet* 2015; 40(3): 295–9.
122. Alsindi A, Murphy C, Martin D. Amiodarone-induced torsades de pointes in a patient with HIV on combination antiretroviral therapy. *Grand Rounds* 2010; 10: 28–33.
123. Renet S, Chaumais MC, Antonini T, Zhao A, Thomas L, Savoure A, et al. Extreme bradycardia after first doses of sofosbuvir and daclatasvir in patients receiving amiodarone: 2 cases including a rechallenge. *Gastroenterology* 2015; 149(6): 1378–1380.e1.
124. Kessler KM, Interian A, Cox M, Topaz O, De Marchena EJ, Myerburg RJ. Proarrhythmia related to a kinetic and dynamic interaction of mexiletine and theophylline. *Am Heart J* 1989; 117(4): 964–6.
125. Nguyen KN, Aursnes I, Kjekshus J. Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *Am J Cardiol* 1997; 79(2): 115–9.
126. Latini R, Santoro E, Masson S, Tavazzi L, Maggioni AP, Franzosi MG, et al. Aspirin does not interact with ACE inhibitors when both are given early after acute myocardial infarction: results of the GISSI-3 Trial. *Heart Dis* 2000; 2(3): 185–90.
127. Oosterga M, Anthonio RL, de Kam PJ, Kingma JH, Crijns HJ, van Gilst WH. Effects of aspirin on angiotensin-converting enzyme inhibition and left ventricular dilation one year after acute myocardial infarction. *Am J Cardiol* 1998; 81(10): 1178–81.
128. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction



- after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992; 327(10): 669–77.
129. Krumholz HM, Chen YT, Wang Y, Radford MJ. Aspirin and angiotensin-converting enzyme inhibitors among elderly survivors of hospitalization for an acute myocardial infarction. *Arch Intern Med* 2001; 161(4): 538–44.
130. Hanna ER, Clark JA. Serotonin syndrome after cardiopulmonary bypass: a case demonstrating the interaction between methylene blue and selective serotonin reuptake inhibitors. *Case Rep* 2014; 2(9): 113–4.
131. Kelesidis T, Kelesidis I. Unexplained high fever in an elderly patient treated with clonidine, duloxetine, and atorvastatin. *Clin Ther* 2009; 31(12): 2894–9.
132. Siller-Matula JM, Trenk D, Krähenbühl S, Michelson AD, Delle-Karth G. Clinical implications of drug-drug interactions with P2Y₁₂ receptor inhibitors. *J Thromb Haemost* 2014; 12(1): 2–13.
133. Khan SU, Lone AN, Asad ZUA, Rahman H, Khan MS, Saleem MA, et al. Meta-analysis of efficacy and safety of proton pump inhibitors with dual antiplatelet therapy for coronary artery disease. *Cardiovasc Revasc Med [In press]* doi: 10.1016/j.carrev.2019.02.002
134. Chen M, Wei JF, Xu YN, Liu XJ, Huang DJ. A meta-analysis of impact of proton pump inhibitors on antiplatelet effect of clopidogrel. *Cardiovasc Ther* 2012; 30(5): e227–233.
135. Melloni C, Washam JB, Jones WS, Halim SA, Hasselblad V, Mayer SB, et al. Conflicting results between randomized trials and observational studies on the impact of proton pump inhibitors on cardiovascular events when coadministered with dual antiplatelet therapy: systematic review. *Circ Cardiovasc Qual Outcomes* 2015; 8(1): 47–55.
136. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2018; 39: 213–60.
137. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* 2016; 134(10): e123–55.
138. D’Ugo E, Rossi S, De Caterina R. Proton pump inhibitors and clopidogrel: an association to avoid? *Intern Emerg Med* 2014; 9(1): 11–22.
139. Food and Drug Administration U.S. Department of Health and Human Services. Concomitant use of ibuprofen and aspirin. *J Pain Palliat Care Pharmacother* 2007; 21(2): 73–4.
140. Ghadban R, Enezate T, Payne J, Allaham H, Halawa A, Fong HK, et al. The safety of morphine use in acute coronary syndrome: a meta-analysis. *Heart Asia* 2019; 11(1): e011142.
141. Kubica J, Kubica A, Jilma B, Adamski P, Hobl EL, Navarese EP, et al. Impact of morphine on antiplatelet effects of oral P2Y₁₂ receptor inhibitors. *Int J Cardiol* 2016; 215: 201–8.
142. Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J* 2011; 32(15): 1854–64.
143. Wiggins BS, Saseen JJ, Page RL, Reed BN, Sneed K, Kostis JB, et al. Recommendations for Management of Clinically Significant Drug-Drug Interactions With Statins and Select Agents Used in Patients With Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation* 2016; 134(21): e468–95.
144. Danielak D, Karaźniewicz-Łada M, Głowska F. Assessment of the Risk of Rhabdomyolysis and Myopathy During Concomitant Treatment with Ticagrelor and Statins. *Drugs* 2018; 78: 1105–12.
145. Takkouche B, Etminan M, Caamaño F, Rochon PA. Interaction Between Aspirin and ACE Inhibitors. *Drug Saf* 2002; 25(5): 373–8.
146. Borghi C, Ambrosioni E, Novo S, Vinereanu D, Ambrosio G, SMILE-4 Working Party. Comparison between zofenopril and ramipril in combination with acetylsalicylic acid in patients with left ventricular systolic dysfunction after acute myocardial infarction: results of a randomized, double-blind, parallel-group, multicenter, European study (SMILE-4). *Clin Cardiol* 2012; 35(7): 416–23.
147. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 2006; 368(9535): 581–8.