EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM Incidence of Major Gastrointestinal Bleeding in Patients with Acute Coronary Syndrome Treated with Dual Antiplatelet and Anticoagulant Ther...

Article · April 2017

CITATION
1

READS
81

8 authors, including:

Marija Vavlukis
Ss. Cyril and Methodius University in Skopje Faculty of Medicine
239 PUBLICATIONS **8,163** CITATIONS
SEE PROFILE

Hajber Taravari
Ss. Cyril and Methodius University in Skopje
36 PUBLICATIONS **24** CITATIONS
SEE PROFILE

Enes Shehu
University Clinic of Cardiology -Skopje
23 PUBLICATIONS **2** CITATIONS
SEE PROFILE

Darko Kitanoski
University clinic of cardiology-Skopje
33 PUBLICATIONS **40** CITATIONS
SEE PROFILE

ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM
Research Article

Incidence of Major Gastrointestinal Bleeding in Patients with Acute Coronary Syndrome Treated with Dual Antiplatelet and Anticoagulant Therapy-Data from the Registry

Marija Vavlukis*, Bekim Pocesta, Hajber Taravari, Enes Shehu, Darko Kitanoski, Ivica Bojovski, Irina Kotlar and Sasko Kedev

Medical Faculty, Ss' Cyril and Methodius University, University Clinic of Cardiology, St. Mother Theresa no. 17, Skopje, Republic of Macedonia

***Corresponding Author:** Marija Vavlukis, Medical Faculty, Ss' Cyril and Methodius University, University Clinic of Cardiology, St. Mother Theresa no. 17, Skopje, Republic of Macedonia.

Received: March 28, 2017; **Published:** April 17, 2017

Abstract

Aim of the study: To investigate the incidence, predictors and prognosis of gastrointestinal bleeding in patients treated for acute coronary syndrome.

Materials and Methods: A retrospective study with data gathered from the registry. We analyzed different variables of STEMI, NSTEMI and unstable angina treated patients: clinical, angiographic, treatment type, medications use, in-hospital outcome. Upper gastrointestinal bleeding was defined as hematemesis and/or melena with Hgb reduction, requiring cessation of antiplatelet or anticoagulant therapy and administration of erythrocyte transfusion and, if needed, upper GIT endoscopy.

Statistical Analysis: Descriptive, comparative, univariate and multivariate linear and/or binary logistic regression analysis. Statistical significance was determined at a 0,05 level.

Results: 874 patients (66,6% males and 33,4% females, mean age 65,7 ± 11,04 y) were analyzed. 75,4% of the patients had STEMI, 12.5% had NSTEMI and 12,1% APNS. The predominant risk factors were: HTA (59.9%), smoking (56,9%), overweight/obesity (66,7%) and DM (27,8%). 11% had previous MI, 11,3% revascularization, 5,3% CVI and 5% had previous GIT symptomatology. Mean eGFR was 93 ml/min, although 16,4% of the patients had eGFR < 60ml/min. Preexisting anemia was registered in 9,7%. 93,6% of STEMI, and 91,6% of NSTEMI/APNS patients received PCI. Regarding the patients medications, 98,4% were treated with ASA, 70% with 600 mg loading dose Clopidogrel, 90,4% with UFH and 18% received H_2 blockers or PPI. For the in-hospital morbidity, 5,6% of the patients had acute heart failure, 2,8% A-V block, 2,6% acute renal failure, 5,4% supraventricular arrhythmias, 6,4% ventricular arrhythmias, 0,8% in-stent thrombosis, and 0,3% of the patients had ischemic CVI. The most frequent bleeding complications were: 9,2% at the vascular access site, 1,5% GI bleedings and 1,6% UG bleedings. Hospital mortality was 6,8%, and the death Hazard Ratio among patients with GIB was 9,34 (CI 2,95-29,5).

Univariate predictors of GIB were: age (beta ,085), BMI (beta -,073), eGFR < 60ml/min (beta -,081), Crusade bleeding risk score (beta ,141), Hgb (beta -,225), urea (beta ,386), old MI (OR 3,715), GPIIb/IIIa inhibitors (OR 9,267), H2/PPI (OR 10,840), anemia (OR 11,712), eGFR < 60 ml/min (OR 6,390), ARF (OR 7645), and supraventricular arrhythmias (OR 5,440). Previous MI (p = 0,010), use of GPIIb/IIIa inhibitors (p=0,031); H2 or PPI (p = 0,000); eGFR < 60 ml/min (p = 0,050); supraventricular arrhythmias (p = 0,002), and anemia prior ACS (p = 0,042) were identified as independent predictors.

Conclusion: GIB is one of the most frequent bleeding complications in patients treated for acute coronary syndrome, associated with a significant in-hospital mortality risk.

Keywords: *Acute Coronary Syndrome; Upper Gastrointestinal Bleeding; Dual Antiplatelet Therapy; Anticoagulant Therapy; Percutaneous Coronary Intervention; Risk Factors; Clinical Outcome; Proton-Pump Inhibitors; H_2 Blockers*

Abbreviations

ACS: Acute Coronary Syndrome; AHF: Acute Heart Failure; A-V Block: Atrial-Ventricular Block; ARF: Acute Renal Failure; APNS: Unstable Angina; CA: Coronary Arteries; CABG: Coronary-Artery-Bypass Surgery; COPD: Chronic Obstructive Pulmonary Disease; CVI: Cerebrovascular Insults; CRF: Chronic Renal Failure; DAPT: Dual Antiplatelet Therapy; DM: Diabetes Mellitus; EF: Ejection Fraction; EGD: Esophagogastroduodenoscopy; GIB: Gastrointestinal Bleeding; GIT: Gastrointestinal Tract; Glycoprotein Gpiib/Iiia Inhibitors; HTA: Arterial Hypertension; HLP: Hyperlipidemia; HR: Heart Rate; STEMI: Myocardial Infarction With ST-Segment Elevation; NSTEMI: Myocardial Infarction Without ST-Segment Elevation; LV: Left Ventricle; LMWH: Low Molecular Weight Therapy; MI: Myocardial Infarction; NSTEMI: Non Stemi MI; PCI: Percutaneous Coronary Interventions; PVD: Peripheral Vascular Disease; PPI: Proton Pump Inhibitors; SBP: Systolic Blood Pressure; STEMI: ST-Segment Elevation MI; UFH: Unfractionated Therapy

Introduction

Percutaneous coronary intervention (PCI) is an effective treatment modality in patients with acute coronary syndrome (ACS), an entity that includes ST-segment elevation and non-ST-segment elevation myocardial infarction (STEMI and NSTEMI), and unstable angina (APNS). Effective ACS treatment includes not only PCI procedures, but also initial and/or concomitant fibrinolytic, antiplatelet and anticoagulant medications. The aforementioned treatments are associated with an increased frequency of bleeding complications, one of them being gastrointestinal bleeding (GIB). As reported in previous observational and randomized trials, this is associated with prolonged hospital stay and increased in-hospital mortality of these patients [1]. In the HORIZONS-AMI study, prevention of post-primary PCI bleeding complications in patients with STEMI early and late stage survival rates, GIB was one of the most important complications following PCI treatment of STEMI patients during a 30-day follow-up period. The 30-day major bleeding complications in this study varied between 4-5%, and a significant portion of them were GIBs [2]. The reported GIB incidence range in ACS patients varies between 1,1% in the study of Ergelen., *et al*. [1], to 2% in the review study of Tanigawa., *et al*. [3], up to 3,5% in the study of Su-Kiat Chua [4]. Peri-PCI bleeding is a major predictor of an adverse outcome, and is associated with increased mortality even after adjustment for confounding factors. Gastrointestinal (GI) bleeding following PCI occurs in 1.0% - 2.7% of the patients, and is associated with significantly higher in-hospital, 30-day, and 1-year mortality. Patients taking dual-antiplatelet therapy (DAPT) are at higher risk of GI bleeding, although registry, case control, and randomized trial data suggest that this risk is significantly reduced by the use of proton pump inhibitors (PPIs) [5].

This emphasizes the importance of risk factors identification and prognosis of major gastrointestinal bleeding in patients treated for acute coronary syndrome.

Materials and Methods

An observational prospective study with data gathered from the registry. We analyzed different variables of STEMI, NSTEMI and unstable angina treated patients: clinical, angiographic, treatment type, medications use, in-hospital outcome. Gastrointestinal bleeding was defined as an upper or lower GIB requiring cessation of antiplatelet or anticoagulant therapy and administration of erythrocyte transfusion and, if needed, upper GIT endoscopy.

Patients' characteristics

This was an observational retrospective study that required no informed consent from the patients because of the study's retrospective design. Data was gathered from the hospital STEMI registry. All consecutive patients in the registry were subjected to analysis. Subject of analysis were patients admitted to our hospital due to an acute coronary syndrome: STEMI, NSTEMI and unstable angina, classification made on the basis of typical angina presentation, ECG characteristics and markers of myocardial injury.

The observed variables were: demographic: age and gender; clinical: risk factors, comorbidities, previous MI, revascularization, baseline renal function, described as GFR calculated with the Cockcroft-Gault Equation, significant renal insufficiency, defined when the estimated glomerular filtration rate was < 60 mL/min per 1.73 m^2, acute renal failure-contrast induced, defined when a 25% increase from the baseline creatinine value was registered after selective coronary angiography, heart failure, defined when an EF < 40% was recorded. The Killip classification was made on the basis of information regarding symptom severity of heart failure during the hospital treatment course, as follows: Killip class I - no evidence of heart failure; Killip class II - mild heart failure with rales involving one-third or less of the lung fields, and systolic blood pressure = 90 mmHg or higher; Killip class III - pulmonary edema with rales involving more than one-third of the lung fields and systolic blood pressure > 90 mmHg; and Killip class IV - cardiogenic shock with any rales and systolic blood pressure < 90 mmHg. The vast majority of patients underwent coronary angiography for diagnosis confirmation, and as a therapeutic intervention. Medications received before (if available) and during the hospital treatment course were recorded, especially: fibrinolytic, antiplatelet, anticoagulant, H_2 blockers and PPI. Hemogram and biochemistry data were recorded, and anemia was defined when the hemoglobin level was < 110 g/L.

Cardiac catheterization

Percutaneous transracial approach and standard angioplasty technique were used in all patients. Patients without prior antiplatelet therapy were pretreated with oral acetylsalicylic acid 300 mg, clopidogrel 300/600 mg, and intravenous heparin (70 - 100 units/kg), small portion with LMWH. If stent implantation was needed, the intravenous heparin infusion was continued for 24h after stenting or upon the clinicians' decision, as was administration of platelet GP IIb/IIIa receptor inhibitors. After the procedure, all patients were treated with oral acetylsalicylic acid 100 mg and clopidogrel 75 mg daily. Small portion of the patients were not subjected to an invasive procedure, and were treated only with antiplatelet and anticoagulant therapy, in some of them preceding fibrinolytic therapy.

In-hospital morbidity and mortality was recorded, especially GIB. Gastrointestinal bleeding was defined as clinically evident bleeding, including hematemesis, hem-positive coffee ground emesis, hem-positive melena, or a > 20 g/L decrease in hemoglobin levels, necessitating an intervention such as erythrocyte transfusion and/or upper gastroendoscopy.

We presented the patients' characteristics in general, and as a comparison between genders. We also compared and presented the characteristics with statically significant differences between study patients with and without gastrointestinal bleeding, and assessed the independent correlates of gastrointestinal bleeding.

Statistical analysis

We used descriptive statistics; categorical variables were expressed as absolute numbers and percentages; continuous variables were presented as means and standard deviations (mean ± SD). Chi-square test was used for categorical variables, and Pearson's chi-square test was used to assess the significance of the differences. Fisher's exact test for 2x2 square distribution, risk estimate with a 95% confidence interval (95% CI), and Mantel-Haenszel common odds ratio estimate were used to test the significance of OR. Independent samples t-test was used for comparison of the continuous variables. To evaluate the relationship between different variables and outcomes, we performed an univariate linear and/or binary logistic regression analysis. To identify the independent prognosticators of GIB we used a multivariate logistic regression analysis - backward conditional. All analyses were performed using SPSS version 23. A two-sided P-value < 0.05 was considered statistically significant.

Results and Discussion

We analyzed 874 patients treated for acute coronary syndrome during the period from 2012 to 2016. The patients' mean age was 65,7±11,0 years, and 33,4% of them were females. The predominant risk factors were: overweight and/or obesity (67% of the pts), hyper-

tension (nearly 60% of the pts), with OR 1,825 for females, cigarette smoking (57% of the pts), with OR 2,096 for males, diabetes mellitus (28% of the pts), with OR 3,092 for females, known HLP (18% of the pts). 11% of the patients had previous MI, and the same percentage of patients had previous revascularization. The mean EF was 51,3±9,6%, with 16% of the patients having an eGFR <60ml/min, with OR 3,212 for females. With respect to ACS, STEMI patients predominated (75%). 93,6% of STEMI patients and 91,6% of NSTEMI/APNS patients received PCI treatment (Table 1).

Variable	Total	Females (f)	Males (m)	Sig (p)	OR (95% CI)
Gender	874 (100%)	292 (33,4%)	582 (66,6%)	0,000	
Age (years)	65,7 ± 11,0	65,8 ± 11,0	59,9 ± 11,1	0,000	
HTA (+ on treatment)	523 (59,9)	202 (23,1%)	321 (36,8%)	0,000	1,825 (f) (1,356 - 2,457)
HLP	161 (18,4%)	61 (7,0%)	161 (11,4%)	0,108	1,273 (,893 - 1,815)
Smoking	497 (56,9%)	96 (11%)	401 (45,9%)	0,000	2,096 (m) (1,173 - 2,491)
DM	243 (27,8%)	127 (14,5%)	116 (13,3%)	0,000	3,092 (f) (2,272 - 4,208)
• tbl	138 (15,8%)	68 (7,8%)	70 (8,0%)		
• Insulin	105 (12%)	59 (6,8%)	46 (5,3%)		
COPD	25 (2,9%)	13 (1,5%)	12 (1,4%)	0,040	2,213 (f) (,997 - 4,914)
Thyroid dysfunction				0,001	
• Hyperthyroidism	3 (0,3%)	1 (0,1%)	2 (0,2%)		
• Hypothyroidism	10 (1,1%)	9 (1,0%)	1 (0,1%)		
Old MI	96 (11%)	22 (2,5%)	74 (8,5%)	0,012	1,688 (m) (1,071 - 2,659)
Previous revascularization				0,442	2,096 (m) (1,763 - 2,491)
• PCI	100 (11,4%)	28 (3,2%)	72 (8,2%)		
• CABG	9 (1%)	2 (0,2%)	7 (0,8%)		
Chronic renal failure (CRF)	14 (1,6%)	7 (0,8%)	(0,8%)	0,149	2,018 (,701 - 5,807)
PVD	14 (1,6%)	6 (0,7%)	8 (0,9%)	0,311	1,505 (,517 - 4,379)
Carotid disease	6 (0,7%)	1 (0,2%)	4 (0,5%)	0,679	0,997 (0,181 - 5,473)
Previous CVI	46 (5,3%)	21 (2,4%)	25 (2,9%)	0,052	1,726 (0,949 - 3,140)
GIT symptomatology	44 (5%)	14 (1,6%)	30 (3,4%)	0,480	1,075 (0,579 - 1,996)
History of malignant disease	18 (2,1%)	7 (0,8%)	11 (1,3%)	0,394	1,275 (0,489 - 3,324)
Weight (kg)	78,7 ± 12,7	71,9 ± 12,3	82,1 ± 11,5	,000	
Hight (cm)	170,3 ± 9,8	162,0 ± 5,8	174,4 ± 8,6	,000	
BMI	26,8 ± 3,4	27,2 ± 4,2	26,6 ± 2,9	,015	
HR (bpm)	83,7 ± 20,9	87,1 ± 22,6	81,9 ± 19,9	,001	
SBP (mmHg)	139,1 ± 29,2	140,1 ± 30,6	138,7 ± 28,5	,512	
EF (%)	51,3 ± 9,6	52,3 ± 9,8	50,8 ± 9,6	,120	
BMI categorical				,437	
• 0 (< 18,9)	4 (0,5%)	1 (0,1%)	3 (0,4%)		
• 1 (19 - 25)	266 (32,8%)	97 (11,9%)	169 (20,8%)		
• 2 (> 25,1)	542 (66,7%)	174 (21,4%)	368 (45,3%)		
eGFR (ml/min)	93,3 ± 33,6	82,3 ± 34,0	98,931,96	0,000	
eGFR class				0,000	3,212 (2,161 - 4,773) (f)
• 0 > 60ml/min	628 (83,6%)	183 (24,4%)	445 (59,2%)		
• 1 < 60ml/min	123 (16,4%)	70 (9,4%)	53 (7,0%)		
Creatinine (µmoll/L)	76,3 ± 22,1	75,2 ± 27,7	76,9 ± 18,8	0,745	
Urea (mmoll/L)	5,7 ± 2,1	6,1 ± 2,1	5,5 ± 2,1	0,233	
Sodium (mmoll/L)	137,5 ± 3,6	137,4 ± 4,5	137,6 ± 3,1	0,860	
Potassium (mmoll/L)	4,2 ± 0,6	4,1 ± 0,6	4,3 ± 0,5	0,050	
Er ($x10^9$/L)	4,7 ± 0,4	4,4 ± 0,4	4,8 ± 0,4	0,000	
Hgb (g/L)	142,6 ± 15,8	131,4 ± 15,1	148,7 ± 12,6	0,000	
PLT ($x10^6$/L)	230,8 ± 67,8	252,9 ± 70,8	218,9 ± 63,6	0,035	
Le ($x10^6$/L)	11,4 ± 3,6	11,5 ± 3,2	11,3 ± 3,8	0,881	
Glycaemia (mmoll/L)	9,5 ± 4,8	11,1 ± 5,6	8,6 ± 4,1	0,026	
STEMI	659 (75,4%)	216 (24,7%)	443 (50,7%)	0,777	
NSTEMI	109 (12,5%)	38 (4,3%)	71 (8,7%)		
APNS	106 (12,1%)	38 (4,3%)	68 (7,8%)		
Coronary angiography				0,001	0,426 (0,252 - 0,419)
• Yes	813 (93%)	260 (29,7%)	553 (63,3%)		
• No	61 (7%)	32 (3,7%)	29 (3,3%)		
NR of diseased vessels	1,8 ± 1,1	1,8 ± 1,0	1,8 ± 1,1	0,517	
Syntax score	16,4 ± 8,7	17,0 ± 8,9	16,1 ± 8,7	0,362	
STEMI treatment				0,028	
• Primary PCI	594 (89,8%)	188 (28,5%)	405 (61,4%)		
• Facilitated PCI	19 (2,9%)	4 (0,6%)	15 (2,3%)		
• Rescue PCI	6 (0,9%)	2 (0,3%)	3 (0,6%)		
• Medical treatment	29 (4,4%)	17 (2,6%)	11 (1,8%)		
• CABG recomm.	12 (3,3%)	5 (0,6%)	9 (1,5%)		
NSTEMI/APNS treatment				0,248	
• < 24h	151 (70,2%)	56 (26,0%)	95 (44,2%)		
• < 72h	46 (21,4%)	13 (6,0%)	33 (15,3%)		
• CABG recomm.	18 (8,4%)	7 (4,2%)	9 (4,2%)		
CRUSADE bleeding risk score				0,000	
• NSTEMI	24,815,25				
• APNS	24,3 ± 14,9	36,2 ± 13,3	18,7 ± 12,4	0,291	
	27,1 ± 16,7				

Table 1: *General characteristics and gender differences of the study population.*

Legend: ACS: acute coronary syndrome; APNS: unstable angina; BMI: body mass index; CA: coronary arteries; CABG: coronary: artery: bypass surgery; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease; CVI: cerebrovascular insultus; DM: diabetes mellitus; EF: ejection fraction; Er: erythrocyte; GIT: gastrointestinal tract; HTA: arterial hypertension; HLP: hyperlipidemia; HR: heart rate; Le: leucocyte; MI: myocardial infarction; NSTEMI: non ST: elevation MI; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; PLT: platelets; SBP: systolic blood pressure; STEMI: ST: segment elevation MI.

With respect to medications use, 4% of our patients were treated with fibrinolytic therapy. 90,4% of the patients were treated with an UFH loading dose (70 - 100 IU/kg), and 9,6% with LMWH (enoxaparin). 98,4% of the patients were on DAPT (100 mg Aspirin + Clopidogrel), 69% receiving 600 mg loading dose and 16,2% 300 mg loading dose, and in 3,4% of the patients GPIIb/IIIa inhibitors were co-administered. Only 18% of the patients received either H_2 blockers or PPIs (Figure 1).

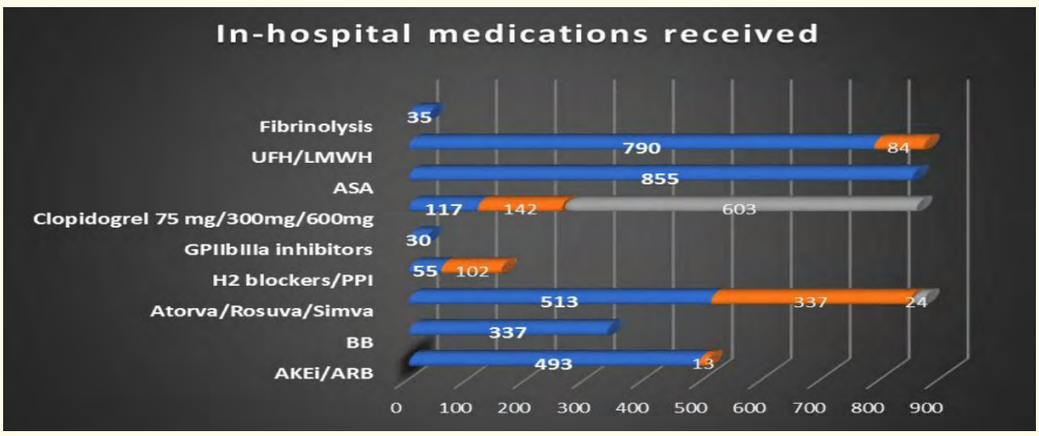

Figure 1: *Medications used during the in- hospital treatment course.*

Legend: ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; ASA: acetylsalicylic acid; BB: beta blockers; Clopidogrel: no loading dose, 300, 600 mg loading dose; LMWH: low molecular weight heparin; PPI: proton pump inhibitors; UFH: unfractionated heparin.

With respect to in-hospital morbidity, the most frequent were bleeding complications (9,2% of the pts). Preexisting anemia was defined as Hgb level < 110 g/L (for both sexes). Access site minor bleeding were registered in 5,2% of the patients (all of our study patients had radial access site). With some differences from the literature data describing GIB as the most frequent major bleeding complication, we had the similar distribution between GIB and UGT bleeding complications. In-hospital mortality was 6,8%, two-times higher in the female patients (OR 2,183) (Table 2).

Variable	Total	Females (f)	Males (m)	Sig	OR (95% CI)
AHF Killip I/II Killip III/IV	 825 (94,3%) 45 (5,6%)	 272 (31,2%) 20 (2,3%)	 553 (63,3%) 29 (3,3%)	 0,164	
A - V block	24 (2,8%)	12 (1,4%)	12 (1,4%)	0,066	2,036 (0,903 - 4,589) (f)
ARF	22 (2,6%)	11 (1,3%)	11 (1,3%)	0,077	2,032 (0,870 - 4,744) (f)
Anemia	85 (9,7%)	47 (5,4%)	38 (4,3%)	0,000	2,746 (1,745 - 4,322) (f)
Supraventricular arrhythmias	48 (5,4%)	24 (2,7%)	24 (2,7%)	0,011	2,082 (1,161 - 3,735) (f)
Ventricular arrhythmias	56 (6,4%)	16 (1,8%)	40 (4,6%)	0,262	
Cardiac arrest	28 (3,2%)	4 (0,5%)	24 (2,7%)	0,019	3,010 (1,054 - 8,595) (m)
In - stent thrombosis	7 (0,8%)	2 (0,2%)	5 (0,6%)	0,569	
Ischemic CVI	3 (0,3%)	1 (0,1%)	2 (0,2%)	0,470	
Bleeding complications • Local hematoma • GIB • UGT (hematuria) • Other	79 (9,2%) 44 (5,2%) 13 (1,5%) 14 (1,6%) 8 (0,9%)	43 (5%) 26 (3%) 6 (0,7%) 7 (0,8%) 4 (0,5%)	36 (4,2%) 18 (2,1%) 7 (0,8%) 7 (0,8%) 4 (0,5%)	0,001	
Upper GIB	13 (1,5%)	6 (0,7%)	7 (0,8%)	0,242	1,723 (0,594 - 5,175)
Death	59 (6,8%)	30 (3,4%)	29 (3,4%)	0,003	2,183 (1,284 - 3,714) (f)

Table 2: *Incidence of early in - hospital morbidity and mortality - general and gender specific.*

Legend: AHF: Acute Heart Failure; A: V Block: Atrial: Ventricular Block; ARF: Acute Renal Failure; GIB: Gastrointestinal Bleeding.

Risk factors for GIB

All patients should be evaluated for risk of bleeding before PCI (Class I, Level of Evidence: C).

Bleeding complications in ACS patients, treated either medically or with PCI (predominantly), are recognized as a major risk factor for subsequent mortality. It may lead to mortality directly (because of the bleeding event) or through ischemic complications (because of the withdrawn antiplatelet and/or anticoagulant agents). The risk of bleeding is associated with a significant number of bleeding risk factors: advanced age, low body mass index, chronic renal failure, baseline anemia, the degree of platelet and thrombin inhibition, anticoagulant and antiplatelet therapy, vascular access site, sheath size [6,7]. There is plenty of data gathered from multiple registries, observational and prospective studies that identifies risk factors associated with bleeding complications, especially with gastrointestinal bleeding. The ATOLL study identified: age > 75 years, cardiac arrest, the use of insulin or heparin as independent correlates of major bleeding. The addition or mixing of several anticoagulant medications was an independent risk factor for major bleeding, despite the predominant use of radial access. In this study, patients presenting with major bleeding had significantly higher rates of adverse ischemic complications. The accent feature of this study is that the study population is PCI treated STEMI patients with radial access site. The importance of the aforementioned comes with a previous presumption that switching from femoral to radial access site will probably change the bleeding risk structure. In this study, beside minor bleeding complications associated with the puncture site, the most frequent bleeding site was the gastrointestinal tract [8]. In the retrospective study of STEMI PPCI treated patients performed by Kikkert., *et al*. the identified GIB predictors were: advanced age, previous GI bleeding, use of GP IIB/IIIA inhibitors, anterior infarction and anemia. However, GIB did not lead to a significant increase of subsequent ischemic events, whereas the risk of GI bleeding after the first occurrence was more than doubled [9]. As an addition to these GIB risk factors, increased inotropic requirement, age above 70 years, and impaired renal function were identified as independent predictors in the retrospective study performed on a study population with the same defined characteristics by Ergelen and co-authors [1]. The same findings were presented by Tanigawa., *et al*. in their review article, although they added physiological stress as one of the risk factors. In their review, they cited findings of potential adverse effect of administration of low-dose aspirin to the small intestine [3].

Helicobacter pylori (Hp) infection is associated with increased risk of upper GIB in patients taking aspirin, NSAIDs and DAPT [10,11]. As it is hypothesized, in patients with acute coronary syndrome Hp has dual action/association. Primarily Hp colonizes gastric mucosa, and by increasing its' vulnerability, increases the risk of GIB, especially after exposure to aforementioned medications. Other jet hypothesized mechanism is involvement of Hp infection in the pathogenesis of atherosclerosis via chain of reactions: activation of a systemic and/or local inflammatory reaction, induction of plaque progression and/or instability, enhanced platelet reactivity and increased risk of GIG [10]. The first mechanism was supported by the study of Chan., *et al*. who reported that among patients with Hp infection and a history of upper GIB who were taking low-dose aspirin, the eradication of Hp was equivalent to treatment with omeprazole in preventing recurrent bleeding [12].

ACG Clinical Guideline for Treatment of Helicobacter Pillory Infection, from 2017 recommended testing for Hp infection could be considered for reduction of the risk for upper GIB in patients taking long-term low-dose aspirin. Those who test positive should be offered eradication therapy (conditional recommendation) [13]. One of the recommended strategies in patients scheduled for coronary angiography and potential usage of DAPT is test-and-treat Hp infection [11]. But, in the cohort of patients with acute coronary syndrome this strategy is not applicable, so as recommended in ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, co-therapy with a PPIs is recommended, based on a body of evidences that this strategy reduces upper GIB in this patients' cohort [7].

Testing for Hp was no part of the evaluation in our study cohort as these were ACS patients, which doesn't exclude testing for Hp infection in the follow up period if needed.

The majority of the generally recognized risk factors for bleeding complications, especially for GIB bleeding, were identified as such in our study cohort as well (Table 3).

Variable (continuous)	GIB	Mean ± SD		beta	Sig
Age	No	61,7 ± 11,4		,085	0,006
	Yes	69,8 ± 10,5			
BMI	No	26,9 ± 3,4		-.073	0,038
	Yes	24,8 ± 3,1			
eGFR	No	93,7 ± 33,4		-,081	0,026
	Yes	70,9 ± 42,3			
CRUSADE bleeding risk score	No	24,5 ± 15,1		,141	0,001
	Yes	40,5 ± 15,6			
Hemoglobin	No	143,2 ± 15,3		-,225	0,049
	Yes	121,0 ± 26,9			
Urea (blood)	No	5,6 ± 1,8		,386	0,001
	Yes	10,6 ± 5,5			
Variable (categorical)			**OR**	**CI (95%)**	**sig**
Old MI	No	9	3,715	1,122 - 12,303	0,032
	Yes	4			
GPIIb/IIIa inhibitors	No	27	9,267	2,412 - 35,600	0,001
	Yes	3			
H_2 blockers or PPIs	No	157	10,840	3,294 - 35,667	0,000
	Yes	9			
eGFR class	No	6	6,390	1,919 - 21,281	0,003
<60ml/min	Yes	7			
ARF	No	20	7,645	1,560 - 36,769	0,011
	Yes	2			
Anemia	No	78	11,712	3,840 - 35,714	0,000
	Yes	7			
Supraventricular arrhythmias	No	45	5,440	1,446 - 20,459	0,012
	Yes	3			
Death	No	8	9,340	2,955 - 29,522	0,000
	Yes	5			

Table 3: *Univariate predictors of GIB bleeding complications.*

Legend: ARF: Acute Renal Failure; Egfr: Estimated Glomerular Filtration Rate; MI: Myocardial Infarction.

A multivariate analysis with binary logistic regression model (backward conditional), when all variables identified as statistically significant in the univariate analysis were entered, was made (Chi square 36,701, p = 0,000) with a 98,5% true predictive value, and several independent predictors were identified: previous MI (p = 0,010), use of GPIIb/IIIa inhibitors (p = 0,031); use of H_2 or PPI (p = 0,000); eGFR < 60 ml/min (p = 0,050); supraventricular arrhythmias (p = 0,002); anemia prior ACS (p = 0,042); low body weight (p = 0,019).

GIB is a significant predictor of in-hospital mortality. 5 out of 13 patients that exhibited major GIB had fatal outcome or, in other words, patients that suffered major GIB had 9,340 Hazard ratios for fatal outcome during the in-hospital treatment.

Bleeding risk assessment

Many bleeding risk scores have been developed from registries or trial cohorts in the setting of ACS and PCI.

The group of Badar., *et al*. used the REPLACE risk score to assess GIB risk and use of gastroprotective medications. The REPLACE risk score consists of six variables: age, female gender, eGFR < 60 ml/min, preexisting anemia and use of LMWH in the last 48 hours. The range of this risk score is 0 - 10 [5].

ESC guidelines on NSTEMI treatment from 2011 introduced the CRUSADE bleeding risk score (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines), that was developed from a cohort of 71277 NSTE-ACS patients, and validated in a cohort of 17857 patients. The CRUSADE bleeding risk score determines eight variables: female gender, history of diabetes, history of PVD or stroke, HR, SBP, signs of heart failure, hematocrit and eGFR, to estimate the patients' likelihood of an in-hospital major bleeding event. The model performance for this risk score was defined as modest (C-statistic 0.68 in patients treated conservatively and 0.73 in patients undergoing invasive approach). The Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) bleeding risk score was derived from a cohort of 17421 patients with ACS (both NSTE-ACS and STEMI) recruited in the ACUITY and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trials. Six independent predictors: female gender, advanced age, elevated serum creatinine, white blood cell count, anemia and presentation as NSTEMI or STEMI, and one treatment-related variable (use of UFH and a GPIIb/IIIa inhibitor rather than bivalirudin alone) were identified. However, this risk score has not been validated in an independent cohort, and there is no available model performance for it, as compared to the CRUSADE score. So, even though both scores, CRUSADE and ACUITY, have reasonable predictive values for major bleeding in ACS patients undergoing coronary angiography, the CRUSADE bleeding risk score may be preferred in patients undergoing coronary angiography to quantify bleeding risk. That was done in 2015 Guidelines for NSTEMI patients, where the CRUSADE risk score was first recommended for ACS patients going to coronary angiography, to assess the risk of major bleeding (class of recommendation IIb, level of evidence II) [6].

Changes in the interventional practice, increased use of radial access, reduced UFH dose, bivalirudin use, diminished GP IIb/IIIa inhibitors use, and administration of the more effective $P2Y_{12}$ inhibitors, may modify the predictive value of the risk scores. One should remember that an individual approach to each and every patient needs to be exercised by assessing their ischemic and bleeding risks [6,7].

In our institution, the CRUSADE bleeding risk score is calculated for all ACS treated patients. The mean score for our study cohort was 24,79 ± 15,24, ranging from 1-72, with a 75-percentile distribution of > 35,29. The score comparison between patients who experienced upper GIB and the ones that did not, demonstrated a statistically significant difference (p = 0,001), as presented in Table 4 and Figure 2. In our patient cohort, the discriminant function of the CRUSADE risk score was found to be high (ROC Curve: Area under the Curve .777; p < 0.003 (CI .622 - .932)) (Figure 3), not only in predicting bleeding complications in ACS treated patients, but in specifically predicting GIB as well.

CRUSADE BRS	GIB	N	Mean ± SD	Sig	Beta
	0	535	24,49 ± 15,09	0,001	,141
	1	13	40,50 ± 15,58		
CRUSADE BRS		**%**	**Receiving GPM**	**Sig**	**OR (CI)**
	1 (≥ 41)	16,5%	30%	0,008	1,979 (1,187-3,298)
	GIT medication	**N**	**Mean ± SD**	**Sig**	**Bonferroni Post Hoc**
None	0	437	23,57 ± 14,68	0,001	
H_2 blockers	1	39	30,13 ± 16,08		0 vs 1 0,028
PPI	2	69	29,46 ± 16,88		0 vs 2 0,008

Table 4: *Association of the CRUSADE bleeding risk score with GIB and GIT protection medications. Legend: CRUSADE bleeding risk score (BRS) is constructed of eight variables, that enables us to predict the risk of major in-hospital bleeding: hematocrit, eGFR, HR, SBP, prior vascular disease, diabetes mellitus, chronic heart failure and gender. Classification is as follows: very low risk - <21; low risk -21-30; moderate risk - 31- 40; high risk - 41- 50; very high risk - >50; with maximal score being 100.*

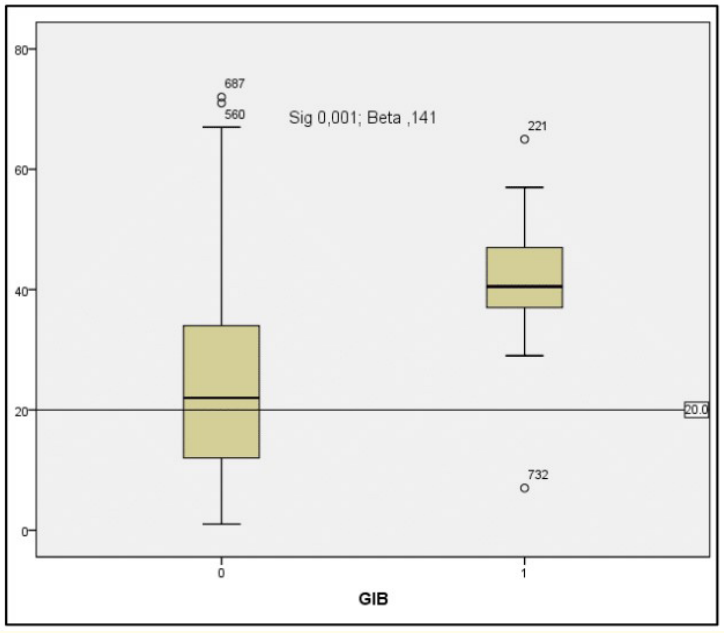

Figure 2: *Distribution of patients across the CRUSADE scores as a function of GIB (left).*

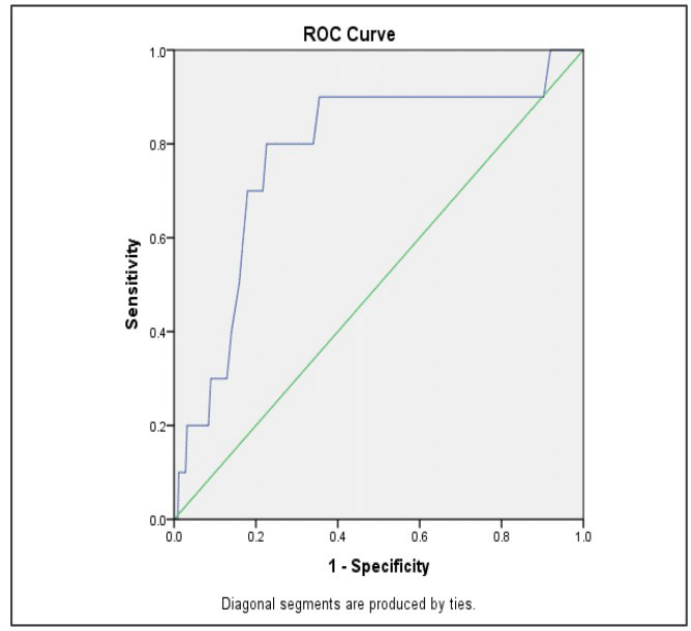

Figure 3: *ROC Curve of the CRUSADE score prediction of GIB.*

Provision of gastroprotective medications in ACS treated patients

There are several points of discussion on this topic, such as: whether H_2 blockers provide better GIT protection in comparison to PPIs, are all PPIs equally protective, do PPIs increase the risk of ischemic events, or interfere with cardiovascular outcomes. Do we prescribe PPIs to all ACS patients treated with dual antiplatelet (DAPT) and anticoagulant and/or fibrinolytic therapy, and for how long?

The answers of these questions are formulated in Clinical Practice Guidelines. ACCF/ACG/AHA guidelines from 2008 initially recommended that all patients on DAPT, or with risk factors for GI bleeding, should receive GI prophylaxis with PPIs (without enough data from randomized trials to support this approach). Focused updates of ACCF/AHA/SCAI guidelines in 2011 continued to recommend PPIs, but now recommendations were based on registry, case control, and randomized trial data, which shows that the risk is significantly reduced by PPIs. So, the 2011 Guidelines recommend PPIs for patients on DAPT and a prior history of GI bleeding (class I, level of evidence C), and are appropriate for patients who have an increased risk of GI bleeding (including those of advanced age, or taking steroids, warfarin or non-steroidal anti-inflammatory drugs) (class IIa, level of evidence C). PPIs are not recommended for routine use in patients at low GI bleeding risk (class III, level of evidence C) [7].

The real-life scenario of gastroprotective medication prescription

Prescribing PPIs for the primary prevention of GI bleeding in ACS treated patients was controversial for a long period of time. In 2009, the MHRA advised against the co-prescription of PPIs and clopidogrel, based on a number of pharmacokinetic studies that demonstrated reduced platelet inhibitory activity of clopidogrel when co-administered with omeprazole. The FDA notes that there is no evidence that other drugs that reduce stomach acid, such as H_2 receptor antagonists (except cimetidine) or antacids, interfere with clopidogrel responsiveness. More data from the registries have shown an association with increased risk of MACE (MI and death) in patients taking this

combination. Then there was a large meta-analysis of 34 observational and prospective studies performed by Melloni., *et al.* that couldn't bring a conclusion to this question [5,14,15].

The COGENT (Clopidogrel and the Optimization of Gastrointestinal Events) trial was a large randomized trial of patients with DAPT (clopidogrel and omeprazole or clopidogrel and placebo), that demonstrated no difference in cardiovascular events between the two groups, with significant reduction in GI events (halved) in those randomized to omeprazole. Data from post hoc analysis of the TRITON-TIMI-38 and PRINCIPLE-TIMI-44 trials shows that PPIs (as a class of medications) reduce major GIB without an increase in ischemic events. In In patients in whom there is a clear indication for PPI therapy, some clinicians may choose to use a PPI other than omeprazole [7].

Regarding the question as to whether H_2 blockers or PPIs offer better gastroprotection in ACS treated patients on DAPT, we have the data from the study of Ng FH., *et al*. published in 2012, that demonstrated superiority of esomeprazole over famotidine in preventing upper GI complications related to aspirin, clopidogrel, enoxaparin or thrombolytics in ACS treated patients [16].

Given our "fear" of worse cardiovascular outcomes associated with PPIs co-administration, it seems that in everyday practice a significant majority of high bleeding risk patients do not receive optimal gastroprotective medications.

In a retrospective analysis performed on over 800 patients with ACS by Badar., *et al*. from 2013, 46,3% of the patients were at a high bleeding risk (REPLACE scores ≥ 10), but less than half of them were provided with an appropriate GI prophylaxis. The study stated that increased use of objective bleeding risk scores may help guide risk/benefit decisions in patients taking clopidogrel who are considered for PPIs [5].

The main criterion for prescribing gastroprotective medication (H_2 blockers or PPI) in our patients' cohort was the Crusade bleeding risk score. Patients that were non-prescribers had a mean score of 23,57 ± 14,68, or borderline between very low/low risk score, and patients that were prescribers had mean score of 29,70 ± 16,52 (low risk), without a statistically significant difference between H2 and PPI receivers. Whenever there was a possibility PPI was prescribed (all patients were treated with pantoprazole). In situations where PPIs were unavailable, H_2 blockers (equally divided between ranitidine and famotidine) were ordinated (Table 4). 13,5% of our study population was in the group of high and very high bleeding risk score, but only 30% of them received gastroprotective medication (Table 4), leading us to conclusion that a significant portion of our patients with high GIB risk remained unprotected.

Safety of esophagogastroduodenoscopy in ACS treated patients

Upper gastrointestinal bleeding in the setting of acute myocardial infarction (MI) has substantial morbidity and mortality. Many studies have been performed on the safety of esophagogastroduodenoscopy (EGD) after MI; however, these studies vary in their results [17]. There is limited guideline and study data regarding the safety of endoscopy in this population [18].

In our study 13 patients suffered from major upper GIB. All of them were subject to invasive procedures, and required transfusion because of significant hemoglobin reduction to a level < 90 g/L. In 9 patients esophagogastroduodenoscopies were undertaken during the hospital stay, usually after erythrocyte transfusion and hemodynamic stabilization, and usually in the first five days after PCI. One death occurred during the esophagogastroduodenoscopy procedure, because of cardiocirculatory failure, leading to cardiac arrest, even though the procedure was performed after 5-6 days of the initial GIB and at the patients' Hgb level of >110 g/L.

In the study of Lim., *et al*. 87 patients underwent EGD within the first 30 days post-MI. No major complications were observed. Minor complications were reported in 27 patients (31.0%), including mild hypotension, mild bradycardia, or increased chest pain. In this study

STEMI patients received statistically significant quicker endoscopy (P = 0.01) and were more likely to undergo cardiac catheterization in advance of EGD (P < 0.01) than those with NSTEMI. No statistically significant differences were observed regarding the minor complications (P = 0.08) among patients with STEMI and NSTEMI. It was concluded that EGD is relatively safe for the diagnosis and management of upper gastrointestinal bleeding in patients with acute MI [17].

Al-Ebrahim., *et al*. in a study performed in a Canadian tertiary center, reported outcomes in 121 patients with MI who underwent endoscopy due to upper GIB within the first 30 days post-MI. The characteristics of the population were as follows: the mean age was 75 years, 55% of the patients were females, the mean hemoglobin level was 86 g/L, and 38 out of 44 patients required a transfusion. Comorbidities included hypertension (82%), diabetes (46%), heart failure (55%), stroke (21%), lung disease (27%), previous MI (46%), cardiac bypass surgery (30%), history of GI bleed (25%), history of ulcer (18%) and ejection fraction <50% (48%). The median number of days to post-MI endoscopy was three. Complications included seven patients with acute coronary syndrome, one with arrhythmia, one with respiratory failure, one with aspiration pneumonia and two with perforation. Age, hemoglobin level or timing of the endoscopy procedure were not identified as significant complication predictors. The authors concluded that endoscopy is a valuable tool in the diagnosis and management of bleeding complications, but must be weighed against the potential risk of other complications, which in their study occurred in more than 25% of the patients treated with EGD [18].

We can conclude that esophagogastroduodenoscopy can be relatively safely performed in patients with acute coronary syndrome, because additional myocardial ischemia resulting from significant anemia is far more dangerous for the patient clinical outcome than the endoscopic procedure per se.

Conclusion

Bleeding complications, even in the era of radial access sites, are by far the most frequent complications in ACS treated patients. Among them, gastrointestinal bleeding predominates, and defines the in-hospital course of the disease, as it significantly increases in-hospital morbidity and mortality. That is why all patients should be timely and appropriately evaluated for risk of bleeding, patients with high bleeding risk should be identified and appropriate protective measures should be undertaken. With respect to GIB, it means prescribing of gastroprotective medications, and if necessary esophagogastroduodenoscopy, as it can be safely performed in this patients' subset.

Conflict of Interest

We declare no conflict of interest of any kind in accordance to this manuscript, its topic and results.

Bibliography

1. Ergelen M., *et al*. "Gastrointestinal bleeding in patients undergoing primary angioplasty for acute myocardial infarction: incidence, risk factors and prognosis". *Turk Kardiyoloji Dernegi Arsivi* 38.2 (2010): 101-106.

2. Stone GW, *et al*. "Bivalirudin during Primary PCI in Acute Myocardial Infarction". *New England Journal of Medicine* 358.21 (2008): 2218-2230.

3. Tanigawa T., *et al*. "Gastrointestinal bleeding after percutaneous coronary intervention". *Digestion* 83.3 (2011): 153-160.

4. Chua SK., *et al*. "Gastrointestinal Bleeding and Outcomes after Percutaneous Coronary Intervention for ST Segment Elevation Myocardial Infarction". *American Journal of Critical Care* 20.3 (2011): 218-225.

5. Badar A., *et al*. "Provision of gastroprotective medication and bleeding risk following acute coronary syndrome". *Journal of Invasive Cardiology* 25.8 (2013): 397-401.

6. Marco Roffi., *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)". *European Heart Journal* 37.3 (2016): 267-315.

7. Levine GN., *et al*. "2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions". Journal of the American College of Cardiology 58.24 (2011).

8. Pellaton C., *et al*. "Incidence and consequence of major bleeding in primary percutaneous intervention for ST-elevation myocardial infarction in the era of radial access: an analysis of the international randomized Acute myocardial infarction Treated with primary angioplasty and intravenous enoxaparin or unfractionated heparin to Lower ischemic and bleeding events at short- and Long-term follow-up trial". *American Heart Journal* 170.4 (2015): 778-786.

9. Kikkert WJ., *et al*. "Predictors and prognostic consequence of gastrointestinal bleeding in patients with ST-segment elevation myocardial infarction". *International Journal of Cardiology* 184 (2015): 128-134.

10. Budzyński J., *et al*. "Clinical significance of Helicobacter pylori infection in patients with acute coronary syndromes: an overview of current evidence". *Clinical Research in Cardiology* 103.11 (2014): 855-886.

11. Chan FK. "Anti-platelet therapy and managing ulcer risk". *Journal of Gastroenterology and Hepatology* 27.2 (2012): 195-199.

12. Chan FK., *et al*. "Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen". *New England Journal of Medicine* 344.13 (2001): 967-973.

13. Chey WD., *et al*. "ACG Clinical Guideline: Treatment of Helicobacter pylori Infection". *American Journal of Gastroenterology* 112.2 (2017): 212-238.

14. Vaduganathan M., *et al*. "Efficacy and Safety of Proton-Pump Inhibitors in High-Risk Cardiovascular Subsets of the COGENT Trial". *American Journal of Medicine* 129.9 (2016): 1002-1005.

15. Melloni C., *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". *Circulation Cardiovascular Quality and Outcomes* 8.1 (2015): 47-55.

16. Ng FH., *et al*. "Esomeprazole compared with famotidine in the prevention of upper gastrointestinal bleeding in patients with acute coronary syndrome or myocardial infarction". *American Journal of Gastroenterology* 107.3 (2012): 389-396.

17. Lim RG., *et al*. "Endoscopy after acute myocardial infarction: an evaluation of safety". *Southern Medical Journal* 106.10 (2013): 545-549.

18. Al-Ebrahim F., *et al*. "Safety of esophagogastroduodenoscopy within 30 days of myocardial infarction: a retrospective cohort study from a Canadian tertiary centre". *Canadian Journal of Gastroenterology* 26.3 (2012): 151-154.

Volume 2 Issue 4 April 2017