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Clopidogrel versus ticagrelor in chronic kidney disease patients presenting with acute coronary syndrome: A retrospective evaluation

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ABSTRACT

Aim: To compare the efficacy and bleeding risk of clopidogrel versus ticagrelor in patients presenting with the acute coronary syndrome (ACS).
Method: This was a single-center retrospective comparison of in-hospital and 1-year major advance cardiovascular events (MACE) in patients with ACS and reduced estimated glomerular filtration rate (eGFR <60 mL/min) who were treated with clopidogrel or ticagrelor in addition to aspirin. Clinicodemographic features, medication use, and laboratory values were recorded. eGFR was calculated by means of the modification of diet in renal disease (MDRD) equation. The Killip classification was used to quantify the severity of heart failure. The primary outcome measures were in-hospital and 1-year MACEs and major and minor bleeding. MACE definition included recurrent myocardial infarction, stroke, and cardiovascular death.
Results: In total, 235 patients (40.9% female, mean age 67.8 ± 12.4 years) were included. Of all patients, 56% presented with ST-elevation myocardial infarction (STEMI), whereas 44% had a non-ST-elevation myocardial infarction. Sixty-eight patients were treated with ticagrelor, while 167 patients were administered clopidogrel. The groups were comparable in terms of in-hospital mortality, cerebrovascular accident (CVA), and re-infarction rates. There was no statistical difference between the mortality, CVA and re-infarction rates between the groups at 12-month. In-hospital minor bleedings were more common among ticagrelor users. In-hospital major bleeding frequencies were similar in both groups. There was no statistical difference in terms of major or minor bleeding rates at 12 months.
Conclusion: The findings of the present study showed comparable efficacy and bleeding risk in ACS patients who were treated clopidogrel or ticagrelor.

Key words: Acute coronary syndrome, bleeding, clopidogrel, major adverse cardiovascular events, ticagrelor.

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Introduction

Acute coronary syndromes (ACS) involving ST-elevation myocardial infarction (STEMI), Non-ST elevation myocardial infarction (NSTEMI), and unstable angina is the leading cause of death in industrialized countries [1, 2]. Around 15% of patients presenting with ACS

succumb to death at the first event. For the rest of the patients, the most crucial part of management is of preventing major cardiovascular adverse events such as recurrent myocardial infarction (MI), death, stroke, and hospitalization. The major way of preventing MACEs after an ACS occurrence is using anti-platelet agents.

The latest American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend immediately starting aspirin and using it indefinitely thereof. The guidelines also favor the use of a P2Y12 inhibitor for at least 12 months in addition to aspirin as a class I recommendation [3].

P2Y12 adenosine receptor inhibitors include clopidogrel, ticagrelor, and prasugrel. Clopidogrel, as the first member of this class, enjoyed widespread use with beneficial effects in terms of curbing MACEs. However, several limitations of clopidogrel including, the requirement of hepatic metabolism for activation, slow onset of action, low bioavailability, variable and unpredictable patient response, led to the development of newer members of P2Y12 inhibitors such as ticagrelor [4].

In contrast to clopidogrel and ticagrelor, prasugrel is not a thienopyridine with a direct and reversible inhibitory effect of P2Y12 adenosine receptor on platelets. It has a quicker onset of action relative to clopidogrel, as well. Ticagrelor was associated with a significantly lower rate of MACEs compared with clopidogrel in patients with ACS in the PLATO trial [5]. Thus, current American guidelines favor the use of ticagrelor or ticagrelor over clopidogrel in patients who did not have an increased risk for bleeding complications [3].

Patients with chronic kidney disease are at increased risk for the development of ACS. Moreover, these patients have a higher risk for both increased coagulation and bleeding compared to patients with normal renal function [6]. The double-edged sword status of impaired kidney function in terms of platelet function is further complicated by excluding patients with significant kidney dysfunction from major randomized controlled trials examining efficacy and safety of antiplatelet agents [7]. Few clinical trials originally dedicated to investigate the performance of P2Y12 inhibitors in patients with impaired kidney function are available or underway [8, 9]. Other post-hoc reports of RCTs or propensity scoring match trials provided conflicting results in terms of the safety and efficacy of P2Y12 inhibitors in patients with ACSs [10, 11]. Thus, we aimed to evaluate, in a retrospective design, the safety and efficacy of ticagrelor in relation to clopidogrel in patients presenting with the acute coronary syndrome.

Materials and methods

Study design, setting, and participants

This was a single-center retrospective comparison of in-hospital and 1-year major advance cardiovascular events (MACE) in patients with acute myocardial infarction and reduced glomerular filtration rate who were treated with clopidogrel or ticagrelor in addition to aspirin. The study period spanned from June 2016 to January 2020. Istanbul Medipol University ethics committee approved the study protocol (Approval ID: E-10840098-772.02-1599). Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the “Declaration of Helsinki” and approved by the institutional ethics committee.

All patients with acute myocardial infarction (both ST elevated and non-ST elevated) during the abovementioned period were screened from the electronic hospital database system. Only patients with estimated glomerular filtration rate (eGFR) <60 mL/min were included in the study. Patients whose eGFR>60 mL/min, who were lost to follow-up after discharge, and had missing data with regards to study parameters were excluded from the study.

Data collection

Clinicodemographic features such as age, gender, comorbid conditions, smoking status, medication use, and laboratory values, including serum hemoglobin level and serum creatinine value, were recorded. Estimated GFR (eGFR) was calculated by means of the Modification of Diet in Renal Disease (MDRD) equation [12]. The Killip classification was used to quantify the severity of heart failure [13]. Based on this classification, patients were categorized into four classes: Killip I, no clinical signs of heart failure; Killip II, bibasilar crackles in the lungs, S3 heart sound, and elevated jugular venous pressure; Killip III, acute pulmonary edema; and Killip IV, cardiogenic shock or arterial hypotension.

Major cardiovascular adverse events (MACEs)

The primary outcome measures of the present study were in-hospital and 1-year MACEs and major and minor bleeding. MACE definition included recurrent myocardial infarction, stroke, and cardiovascular death. Recurrent ST-elevation myocardial infarction was defined as a new occurrence of ischemic symptoms lasting more than 20 minutes with new ST elevation >0.1 mV in more than two contiguous leads along with troponin elevation [14]. Stroke is defined as the occurrence of a new focal neurologic deficit which was considered as of vascular origin along with signs and/or symptoms lasting more than 24 hours. Cranial imaging was not imperative, but when present, supported the diagnosis of stroke [15]. Major bleeding was defined as fatal, leading to symptomatic hypotension, requiring surgery, intracranial hemorrhage, or requirement of ≥ 4 packed red blood cell transfusion [15]. Minor bleeding was defined as bleeding not meeting the major bleeding criteria.

Patient charts and electronic databases were examined thoroughly for the presence of MACEs during the hospitalization period. All study patients had been followed up by our outpatient cardiology clinic after their discharge from the hospital. Thus, for 1-year MACEs, we examined outpatient clinic charts in detail. We evaluated whether clopidogrel or ticagrelor use predicts in-hospital, 12-month, or composite mortality by univariate logistic regression. Since clopidogrel or ticagrelor use did not predict mortality significantly, we did not construct a multivariate logistic regression model.

Statistical analysis

The Shapiro–Wilk test, histogram, and Q-Q plot were used to test the normality of the variables. Normally distributed variables were presented as mean ± standard deviation, and non-normally distributed variables were given as a median and interquartile range. The Independent samples t-test and the Mann–Whitney U test were used for numerical variables in two group comparisons according to the distribution of the variables. The Chi-square test and Fisher's exact test were used to compare the categorical variables between the groups. We performed univariate logistic regression for selected variables. The SPSS 25.0 software package (IBM, Armonk, NY, USA) was used to analyze the data of the study. A *p*-value <0.05 was accepted as statistically significant.

Results

General characteristics of the whole study group

In total, 235 patients (40.9% female and 59.1% male) were included in the study. The mean age was 67.8 ± 12.4 years. The most common chronic condition was hypertension (76.2%), followed by diabetes mellitus (38.3%), coronary artery disease (34%), and hyperlipidemia (17.9%). Table 1 summarizes the general characteristics of the whole study group.

Table 1. Comparison of clinic-demographic characteristics, acute coronary syndrome type, treatment modalities, and laboratory values of patients treated with clopidogrel and ticagrelor.

Parameters	Patients		*p*-value
	Ticagrelor group (n=68)	Clopidogrel group (n=167)	
Age (years)	63.0±11.8	69.8±12.2	<0.001†
Sex (n (%))			
Female	24 (35.3&)	72 (43.1%)	0.307$^{X^2}$
Male	44 (64.7%)	95 (56.9%)	
Comorbidities n (%)			
Coronary artery disease	23 (33.8%)	57 (34.1%)	1.000$^{X^2}$
Hypertension	54 (79.4%)	125 (74.9%)	0.503$^{X^2}$
Dyslipidemia	17 (25.0%)	25 (15.0%)	0.090$^{X^2}$
Diabetes mellitus	31 (45.6%)	59 (35.3%)	0.183$^{X^2}$
Heart failure	8 (11.8%)	26 (15.6%)	0.543$^{X^2}$
Smoking	12 (17.6%)	31 (18.6%)	1.000$^{X^2}$
Killip class			
Class I	49 (72.1%)	100 (59.9%)	
Class II	12 (17.6%)	33 (19.8%)	0.225$^{X^2}$
Class III	3 (4.4%)	10 (6.0%)	
Class IV	4 (5.9%)	24 (14.4%)	
Drugs			
ASA	68 (100%)	165 (98.8%)	0.587$^{X^2}$
Beta-blocker	52 (76.5%)	116 (69.5%)	0.340$^{X^2}$
Statins	65 (95.6%)	131 (78.4%)	0.002$^{X^2}$
ACEI	46 (67.6%)	59 (35.3%)	<0.001$^{X^2}$
Acute myocardial infarction			
NSTEMI	14 (20.6%)	89 (53.3%)	<0.001$^{X^2}$
STEMI	54 (79.4%)	78 (46.7%)	
Treatment of myocardial infarction			
Medical	1 (1.5%)	26 (15.6%)	
CABG	4 (5.9%)	18 (10.8%)	0.002$^{X^2,*}$
PCI	63 (92.6%)	123 (73.7%)	
DES	54 (85.7%)	100 (81.3%)	0.541$^{X^2}$
BMS	9 (14.3%)	23 (18.7%)	
Laboratory parameters			
Creatinine (mg/dL)	1.2 (1.1-1.4)	1.2 (1.1-1.6)	0.259^{m}
Glomerular filtration rate (mL/min)	59 (50-60)	51(36-59)	<0.001^{m}
Hemoglobin (g/dL)	12.3±1.9	11.8±2.4	0.094†
Neutrophil count (10^3/μL)	6.76 (4.92-8.96)	6.7 (5.19-9.53)	0.639^{m}
Lymphocyte count (10^3/μL)	2.08 (1.44-2.70)	1.91 (1.31-2.83)	0.348^{m}
Platelet count (10^3/μL)	254±81	259±74	0.636†
Contrast Nephropathy	17 (25.0%)	45 (26.9%)	0.871$^{X^2}$

*† Independent Samples t Test, $^{X^2}$ Pearson Chi-Square, ^{m} Mann-Whitney U test, *There was significant difference between the groups in terms of medical treatment and PCI. ACEI: Angiotensin-converting enzyme inhibitors, ASA: Acetylsalicylic acid, BMS: Bare metal stent, CABG: Coronary artery bypass grafting, DES: Drug eluting stent, NSTEMI: Non-ST elevation myocardial infarction, STEMI: ST elevation myocardial infarction, PCI: Percutaneous coronary intervention.*

Myocardial infarction

Of all patients, 56% presented with ST-elevation myocardial infarction (STEMI), whereas 44% had non-ST-elevation myocardial infarction (NSTEMI). Percutaneous coronary intervention (PCI) was performed in 186 (79.1%) patients. PCI rates were 92.4% and 62.1% in STEMI and NSTEMI patients, respectively. All patients in STEMI and NSTEMI groups had coronary stent placement. In STEMI patients, the majority of the patients (83.6%), whereas in NSTEMI patients, 81.3% underwent a drug eluting stent (DES) placement. The general treatment approach to the patients with STEMI and NSTEMI is shown in Figure 1.

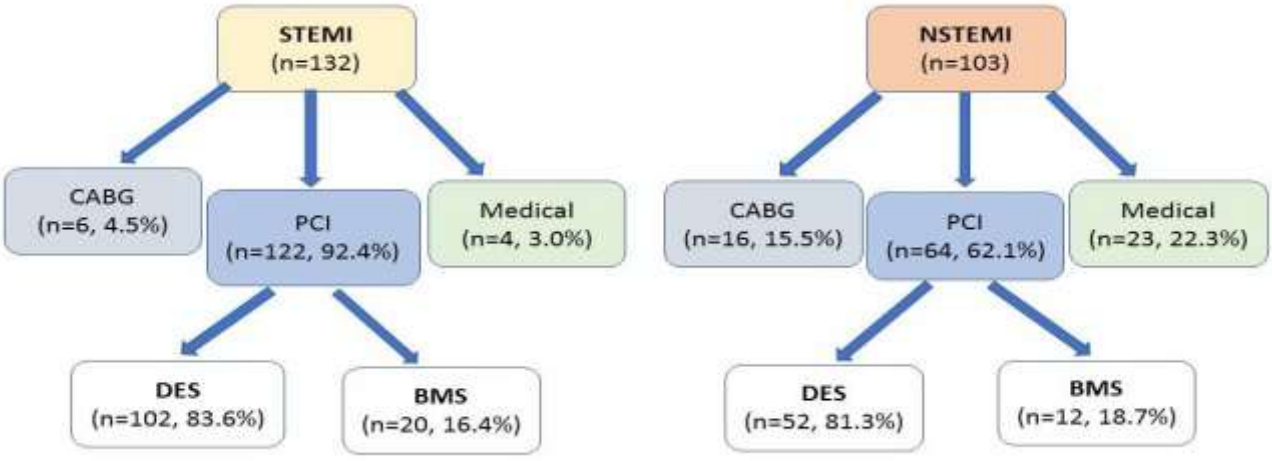

Figure 1. Flow chart of treatment modalities in STEMI and NSTEMI patients.

Features of patients who were treated with clopidogrel or ticagrelor

Sixty-eight patients were treated with ticagrelor, while 167 patients were administered clopidogrel. Gender distribution was comparable; however, the clopidogrel group was composed of significantly older patients. The rates of comorbidities and smoking were not significantly different between the groups. At the baseline evaluation, significantly more patients were using statin and ACE inhibitor in the ticagrelor group relative to the clopidogrel group. Almost all patients were using aspirin before presenting with the acute coronary syndrome (Table 1).

In the ticagrelor group, a significantly higher portion of the group (79.4%) had STEMI compared to patients who were commenced clopidogrel (46.7). As expected, PCI treatment was significantly more common among ticagrelor users (92.6%) compared to clopidogrel users (73.7%).

Although, as per the study design, all included patients had chronic kidney disease (eGFR below 60 mL/min), clopidogrel users had significantly lower eGFR compared to ticagrelor users. None of the patients in either group had stage V chronic kidney disease or receiving dialysis at baseline evaluation.

Major adverse cardiovascular events

Table 2 depicts the rates of MACEs in clopidogrel and ticagrelor groups. Five (7.4%) and 29 (17.4%) patients died during the hospital stay in ticagrelor and clopidogrel groups, respectively (p = 0.064). The groups were comparable in terms of in-hospital cerebrovascular accident (CVA) and re-infarction rates. At the end of the study period (12^{th} month after myocardial infarction), 15 and 41 patients died in ticagrelor and clopidogrel

Table 2. Major Adverse Cardiovascular Events (MACE) and bleeding frequencies in clopidogrel and ticagrelor groups.

Parameters	Patients		*p*-value
	Ticagrelor group (n=68)	Clopidogrel group (n=167)	
MACEs n (%)			
Length of Stay in hospital	2.5 (2-3)	3 (2-4)	0.085[m]
In-hospital mortality	5 (7.4%)	29 (17.4%)	0.064[X²]
In-hospital infarction	1 (1.5%)	4 (2.4%)	1.000[≠]
In-hospital CVA	0	2 (1.2%)	1.000[≠]
In-hospital minor bleeding	5 (7.4%)	3 (1.8%)	0.047[≠]
In-hospital major bleeding	2 (2.9%)	6 (3.6%)	1.000[≠]
12-month mortality	15 (22.1%)	41 (24.6%)	0.738[X²]
12-month reinfarction	13 (19.1%)	49 (29.3%)	0.141[X²]
12-month CVA	3 (4.4%)	10 (6.0%)	0.762[≠]
12-month minor bleeding	3 (4.4%)	10 (6.0%)	0.762[≠]
12-month major bleeding	1 (1.5%)	2 (1.2%)	1.000[≠]
Composite mortality	20 (29.4%)	70 (41.9%)	0.078[X²]

[m] Mann-Whitney U test, [X²] Pearson Chi-Square, [≠] Fisher's exact test. CVA: Cerebrovascular accident, MACEs: Major adverse cardiovascular events.

groups, respectively (p = 0.064). There was no statistical difference between the death, CVA, and re-infarction rates between the groups at 12-month. Neither clopidogrel (p = 0.124) nor ticagrelor use (p = 0.075) was significantly associated with composite mortality in univariate logistic regression.

When we compared the deceased and survivor patients, the mean age was significantly greater in the deceased. The Killip classes III and IV were significantly more frequent in the deceased relative to the survivors. The type of myocardial infarction, treatment modalities, and clopidogrel and ticagrelor use were similar in both groups (Table 3).

Minor and major bleeding

In-hospital minor bleedings were more common among ticagrelor users (5 patients, 7.4%) compared with clopidogrel users (3 patients, 1.8%). In-hospital major bleeding frequencies were similar in both groups. During the 12-month follow-up, 3 (4.4%) and 10 (6.0%) patients experienced a minor bleeding episode. Major bleedings were seen in only one patient in the ticagrelor group and 2 patients in the clopidogrel group. There was no statistical difference in terms of major or minor bleeding rates between the study groups at 12-month evaluation (Table 2).

Discussion

The most notable findings of the present study are as follows: (i) Clopidogrel and ticagrelor were not different in terms of in-hospital recurrent myocardial infarction and mortality. (ii) Patients using clopidogrel and ticagrelor had similar 12-month recurrent MI and mortality. (iii) In-hospital minor bleeding was significantly more common in ticagrelor users. Otherwise, in-hospital major bleeding and 12-month minor and major bleeding rates were similar in both groups.

Ticagrelor has been compared with clopidogrel in several different clinical settings. The recent ALPHEUS study found similar efficacy of ticagrelor and clopidogrel in the prevention of

Table 3. Comparison of patient characteristics between survivor and decedent patients.

Parameters	Patients		*p*-value
	Survivor (n=145)	Decedents (n=90)	
Age (years)	65.1±12.5	72.2±11.1	<0.001†
Sex (n (%))			
Female	59 (40.7%)	37 (41.1%)	1.000$^{X^2}$
Male	86 (53.9%)	53 (58.9%)	
Comorbidities (n (%))			
Coronary artery disease	46 (31.7%)	34 (37.8%)	0.396$^{X^2}$
Hypertension	122 (84.1%)	57 (63.3%)	<0.001$^{X^2}$
Dyslipidemia	31 (21.4%)	11 (12.2%)	0.082$^{X^2}$
Diabetes mellitus	59 (40.7%)	31 (34.4%)	0.408$^{X^2}$
Heart failure	18 (12.4%)	16 (17.8%)	0.340$^{X^2}$
Smoking	29 (20.0%)	14 (15.6%)	0.488$^{X^2}$
Killip class			
Class I	119 (82.1%)	30 (33.3%)	
Class II	22 (15.2%)	23 (25.6%)	<0.001$^{X^2,*}$
Class III	3 (2.1%)	10 (11.1%)	
Class IV	1 (0.7%)	27 (30.0%)	
Drugs			
ASA	145 (100%)	88 (97.8%)	0.146$^{\neq}$
Beta-blocker	122 (84.1%)	46 (51.1%)	<0.001$^{X^2}$
Statins	133 (91.7%)	63 (70.0%)	<0.001$^{X^2}$
ACEI	81 (55.9%)	24 (26.7%)	<0.001$^{X^2}$
Acute myocardial infarction			
NSTEMI	67 (46.2%)	36 (40.0%)	0.417$^{X^2}$
STEMI	78 (53.8%)	54 (60.0%)	
Treatment of myocardial infarction			
Medical	12 (8.3%)	15 (16.7%)	
CABG	12 (8.3%)	10 (11.1%)	0.091$^{X^2}$
PCI	121 (83.4%)	65 (72.2%)	
DES	97 (80.2%)	57 (87.7%)	0.226$^{X^2}$
BMS	24 (19.8%)	8 (12.3%)	
Antithrombotic drugs			
Ticagrelor	48 (33.1%)	20(22.2%)	0.078$^{X^2}$
Clopidogrel	97 (66.9%)	70 (77.8%)	
Glomerular filtration rate (mL/min)	54 (46.5-60)	47.5 (30.8-59.3)	0.002^{m}

† Independent Samples t Test, $^{X^2}$ Pearson Chi-Square, $^{\neq}$ Fisher's exact test, ^{m} Mann-Whitney U test, ACEI: Angiotensin-converting enzyme inhibitors, ASA: Acetylsalicylic acid, BMS: Bare metal stent, CABG: Coronary artery bypass grafting, CVA: Cerebrovascular accident, DES: Drug eluting stent, MACEs: Major adverse cardiovascular events, NSTEMI: Non-ST elevation myocardial infarction, STEMI: ST elevation myocardial infarction, PCI: Percutaneous coronary intervention.

periprocedural MI in patients undergoing elective PCI with significantly more minor bleedings in the ticagrelor arm [16]. In another randomized controlled trial, Park et al. demonstrated that ticagrelor treatment was associated with a higher incidence of major bleeding at 12 months compared with clopidogrel in patients with ACS managed

invasively [17]. A very recent meta-analysis involving studies comparing ticagrelor and clopidogrel in ACS treated with PCI revealed similar rates of ischemic events and mortality in both drugs [18]. However, hemorrhagic events were more frequent with ticagrelor use. On the other hand, in another meta-analysis, Wang and colleagues found similar efficacy and safety for clopidogrel and ticagrelor [18]. These discrepancies might stem from various patient characteristics, treatment modalities, and definitions of the outcomes across different studies.

Chronic kidney disease comprises a significant portion of patients (up to 40%) who presented with ACS [19]. Despite this high incidence, most trials evaluating the safety and efficacy of antiplatelet agents in ACS patients excluded these patients. Increased inflammation, accelerated atherosclerosis, tendency to both coagulation and bleeding makes the clinical outcomes of these patients grimmer when they present with ACS [20]. Patients with CKD have high on-treatment platelet reactivity and thus require more potent antiplatelet agents to avoid recurrent ischemic events [21]. ACS patients who had CKD had a higher risk for stent thrombosis compared with patients without CKD. Thus, it seems plausible that particularly CKD patients require potent P2Y12-ADP antagonists more than ones without CKD. Subgroup analyses of the PLATO trial showed a favorable risk-benefit ratio for ticagrelor use compared with clopidogrel in patients with CKD [22]. However, the limited number of patients with advanced stages of CKD in this trial should be born in mind. The study by Edfors in which clopidogrel was compared with ticagrelor in CKD patients with ACS revealed beneficial effects of ticagrelor in terms of death, myocardial infarction, and stroke at 1-year in patients with moderate but not severe chronic kidney disease [23]. For moderate CKD, the bleeding complication rates were similar for both drugs.

Patients with chronic kidney disease are at increased risk for bleeding because of impaired platelet function by uremic toxins. This risk increases as the kidney function deteriorates further. Thus, theoretically, it is plausible to expect higher bleeding risk with the use of potent antiplatelet agents in these patients. However, the available evidence points to the contrary. RENAMI and BleeMACS projects showed that patients with renal insufficiency, defined as eGFR below 60 mL/min, had significantly higher mortality and re-infarction rates as well as major bleeding in patients with ACS treated with dual antiplatelet agents. On the other hand, in the project, it was reported that strong P2Y12 antagonists (ticagrelor or clopidogrel), significantly reduced mortality and re-infarction rates without an increase in major bleeding incidence [8]. A meta-analysis involving more than 30.000 CKD patients who presented with ACS revealed no increase in bleeding rates with the use of ticagrelor or ticagrelor [24]. One small study in China confirmed the latter findings even in patients with end-stage kidney disease presented with ACS [11].

In our study, we evaluated both in-hospital and out-of-hospital bleeding at 1 year. In-hospital minor bleeding was significantly more common among patients treated with ticagrelor. However, major in-hospital bleeding rates were comparable in both groups. At one year, minor and major bleeding rates were similar in patients treated with clopidogrel and ticagrelor. Several limitations of the present study deserve mention. First, the design of our study was retrospective; thus, we might have missed some minor bleeding episodes. Second, our patient number was relatively small compared with the

posthoc analyses of RCTs published before. Third, our groups were not matched in terms of some important aspects which had the potential to affect the study outcomes.

In conclusion, the findings of the present study showed comparable efficacy and bleeding risk in acute coronary syndrome patients who were treated clopidogrel or ticagrelor.

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