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Comparison of Clopidogrel With Prasugrel and Ticagrelor in Patients With Acute Coronary Syndrome: Clinical Outcomes From the National Cardiovascular Database ACTION Registry

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Abstract

Background: We aimed to compare the clinical outcomes of clopidogrel, prasugrel, and ticagrelor in clinical practice using the National Cardiovascular Database ACTION Registry®. Treatment guidelines for patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention recommend dual antiplatelet therapy (DAPT) for 12 months. Few clinical trials have compared the safety and efficacy of clopidogrel with that of newer antiplatelet therapies.

Methods: A retrospective study of patients hospitalized for ACS at Cleveland Clinic Akron General was conducted. Data elements included detailed medical history and clinical outcomes during hospital stay. The primary outcome was a composite of major clinical events (cardiogenic shock, atrial fibrillation, ventricular fibrillation, ventricular tachycardia, heart failure, bleeding, and mechanical ventilation). The independent variable was the type of DAPT. Statistical analyses were performed using Chi-square and Mann-Whitney U tests. A *post-hoc* analysis was performed to compare between the antiplatelet drugs head-to-head.

Results: Subjects (n = 1,388) admitted between January 2011 and March 2016 with ACS and treated with clopidogrel, prasugrel, or ticagrelor were included in the study. Mean age was 65 ± 14 years and 46% had ST-segment elevation myocardial infarction. Prasugrel administration within 24 h was associated with a lower incidence of the composite outcome (P = 0.049), bleeding (P = 0.028), and heart failure (P = 0.002).

Conclusion: There was a significant difference between the type of antiplatelet drug and clinical outcomes in ACS patients who were treated with DAPT. Observations from current study may provide important information for prescribers in clinical decision-making.

Keywords: Antiplatelet therapy; Coronary artery disease; Health care outcomes

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Introduction

About 1.1 million people in the United States are diagnosed every year with acute coronary syndrome (ACS) [1]. Despite advances in prevention, diagnosis, and management, myocardial infarction remains a common cause of death, disability, poor quality of life, and preventable health-care expenditure worldwide [2]. There has been a search for the ideal antiplatelet agent to accompany aspirin as part of dual antiplatelet treatment in patients with ACS with and without ST-segment elevation myocardial infarction (STEMI) [3].

Current treatment guidelines for patients with ACS undergoing percutaneous coronary intervention (PCI) recommend dual antiplatelet therapy (DAPT), a combination of aspirin and a P2Y12 inhibitor, for at least 12 months after the ACS event [3-6]. DAPT is crucial to prevent major adverse events, such as cardiovascular death, myocardial infarction (MI), stroke, and stent thrombosis in patients with ACS [7]. Clopidogrel remains the P2Y12 inhibitor used most widely; however, incremental benefits compared with clopidogrel have been shown with the more potent P2Y12 inhibitors, e.g. prasugrel and ticagrelor [8, 9].

In contrast to clopidogrel, ticagrelor and prasugrel have faster onset of action and have less inter-individual variation with respect to drug effects [10-12]. Ticagrelor has another advantage in that it is direct acting and reversible [13]. Advantages of ticagrelor and prasugrel make them more suitable for the treatment of patients with a high thrombotic risk. However, the matter gets complicated when patients have both a high thrombotic and bleeding risk [9, 11] in which cases prescribers tend to pick the safest drug. Prasugrel was proven in recent clinical trials to be more efficacious than clopidog-

Table 1. Association Between Baseline Characteristics and Composite Clinical Outcome

Characteristics	n = 1,388	P-value
Age, years (mean ± SD)	63 ± 14	< 0.001*
Female gender (%)	34	0.067
Caucasian (%)	83	0.43
Body mass index (kg/m^2) (mean ± SD)	30 ± 8	0.055
STEMI EKG (%)	46	0.003*
History of heart failure (%)	13	< 0.001*
Diabetes (%)	31	0.032*
Dyslipidemia (%)	61	0.047*
Hypertension (%)	72	< 0.001*
Peripheral arterial disease (%)	10	0.22
Prior coronary artery bypass surgery (%)	18	0.32
Prior myocardial infarction (%)	29	0.083
Prior PCI (%)	27	0.64
History of stroke (%)	9	0.008*
History of transient ischemic attack (%)	2	0.01*
History of cerebrovascular disease (%)	14	0.01*
Dialysis-dependent end-stage renal disease (%)	1.5	0.52
Current tobacco use (%)	39	0.061

*Statistical significance.

rel, with reduced ischemic events, but with increased major bleeding, including fatal bleeding [9, 11]. In a large phase 3 trial of ACS patients with or without STEMI, ticagrelor reduced death from vascular causes, MI, or stroke compared to clopidogrel [11]. In addition, there was no difference in major bleeding events between the two groups, but there was an increase in non-procedure related bleeding events in patients receiving ticagrelor [11].

Guidelines of the American Heart Association/American College of Cardiology and the European Society of Cardiology recommend ticagrelor or prasugrel over clopidogrel for patients with ACS undergoing PCI who can take these drugs safely [3, 5, 6, 14]. Both prasugrel and ticagrelor have been assigned a class 1B recommendation for patients with ACS, especially for those undergoing PCI [15].

There have been few studies comparing the safety and efficacy of clopidogrel with that of prasugrel and ticagrelor [7, 9, 11, 16]. We aim to compare between the type of antiplatelet drug (clopidogrel, prasugrel, or ticagrelor) and the clinical outcomes during hospital stay in a clinical practice using a single-center registry through the National Cardiovascular Database ACTION Registry®. We also performed a head-to-head comparison between antiplatelet drugs using *post-hoc* analysis.

Materials and Methods

A retrospective cohort study of patients hospitalized for ACS and prescribed aspirin plus either clopidogrel, prasugrel, or ticagrelor was conducted using the ACTION Registry® at Cleveland Clinic Akron General. Data elements included all inpatient encounters within the facility, with detailed medical history, medications, and clinical outcomes during hospital stay. Informed consent was waived, as this was a chart review study with de-identified patient data. The study was approved by the local Institutional Review Board.

Adult patients (aged ≥ 18 years of age) who had an index hospital admission and discharge between January 2011 and March 2016, with the diagnosis of ACS were identified. Patients who were treated with aspirin and clopidogrel, prasugrel, or ticagrelor within 24 h of admission were included in the analyses.

Baseline information included demographic data, and comorbidities (hypertension, smoking status, heart failure, dyslipidemia, diabetes mellitus, history of MI, atrial fibrillation, atrial flutter, prior PCI, prior coronary bypass surgery, cerebrovascular disease, stroke or transient ischemic attack, peripheral vascular disease, and dialysis-dependent end-stage renal disease) were identified via diagnosis-related data from hospitalization records. The type of ACS was classified based on electrocardiogram (EKG) findings (ST-segment elevation, new or presumed new left bundle branch, ST-segment depression or T-wave changes, or no EKG changes).

The primary outcome was a composite of major adverse clinical events within the hospital consisting of the patient having at least one of the following: cardiogenic shock, atrial fibrillation, ventricular fibrillation, ventricular tachycardia, heart failure, bleeding, and mechanical ventilation. Bleeding included retroperitoneal, gastrointestinal, and genitourinary

Table 2. Comparison Between Antiplatelet Drugs and Clinical Outcomes

Outcome	Clopidogrel (n = 1,012)	Prasugrel (n = 244)	Ticagrelor (n = 142)	OR (95% CI) (clopidogrel to prasugrel)	OR (95% CI) (clopidogrel to ticagrelor)
AF (%)	5	0	6	-	0.73 (0.22 - 2.45)
VT/VF (%)	4	9	9	0.44 (0.09 - 2.23)	0.42 (0.14 - 1.25)
MV (%)	2	0	3	-	0.49 (0.08 - 2.98)
CS (%)	4	6	5	0.76 (0.41 - 1.42)	0.83 (0.37 - 1.88)
HF (%)	10	4	5	2.96 (1.47 - 5.94)*	2.02 (0.92 - 4.45)
Bleeding (%)	4	1	3	5.5 (1.32 - 22.85)*	1.45 (0.51 - 4.12)
Composite event (%)	15	9	16	1.76 (1.1 - 2.81)*	0.92 (0.56 - 1.51)

*Odds ratio (OR) with statistical significance (P < 0.05). "-" denotes where ORs are undefined and therefore could not be computed. AF: atrial fibrillation; VT/VF: ventricular tachycardia/ventricular fibrillation; MV: mechanical ventilation; CS: cardiogenic shock; HF: heart failure; OR: odds ratio; CI: confidence interval.

bleeding. Each individual clinical event was included in separate analyses as secondary outcomes.

Statistical analysis

Chi-square, for categorical variables, and Mann-Whitney U tests, for continuous variables, were used to determine if the composite clinical event was dependent on baseline characteristics (e.g. demographics, comorbidities, medication use, EKG findings, etc.). In addition, Chi-square tests (2 × 3) were used to determine if the composite and individual clinical events were dependent on antiplatelet type (clopidogrel, prasugrel, and ticagrelor); *post-hoc* analyses were performed using standardized (adjusted) Pearson's residuals with a Bonferroni correction. Where appropriate, Fisher's exact tests and Yate's Chi-squared tests were used. In addition, odds ratios (ORs) with 95% confidence intervals (CIs) were also calculated. A significance level of 0.05 was used for all statistical analyses.

Results

We identified 1,388 adult patients hospitalized and discharged with the diagnosis of ACS and were treated with aspirin and an oral antiplatelet medication (clopidogrel, prasugrel, or ticagrelor) within 24 h of admission. A total of 1,012 patients received clopidogrel, 244 patients received prasugrel, and 132 patients received ticagrelor. Fourteen percent of total patients had the incidence of composite clinical outcome, 1% developed atrial fibrillation, 1.2% developed ventricular fibrillation or ventricular tachycardia, 0.4% placed on mechanical ventilation support, 5% developed cardiogenic shock, 8.6% developed heart failure, and 3.6% developed bleeding.

Key patient baseline demographic and clinical characteristics are summarized in Table 1.

When antiplatelet drugs were compared head-to-head,

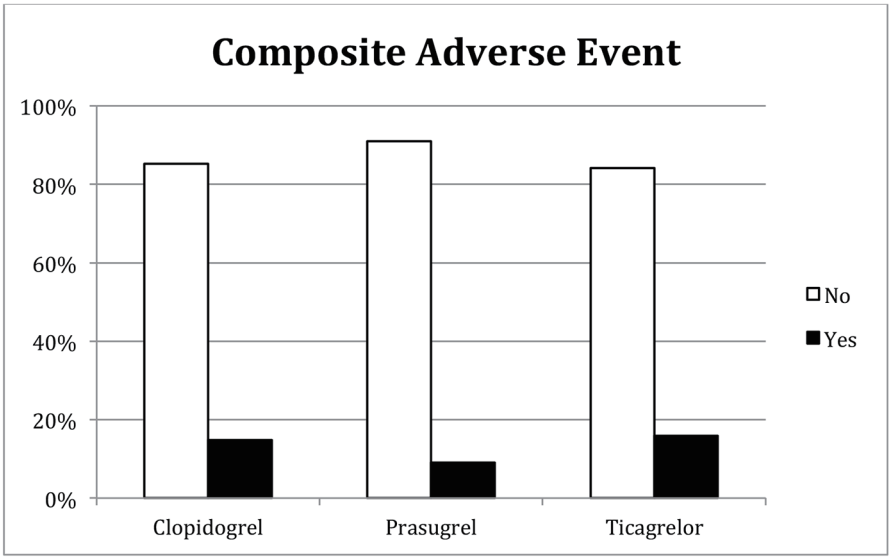

Figure 1. Comparison between antiplatelet drugs for clinical outcome of the composite adverse event.

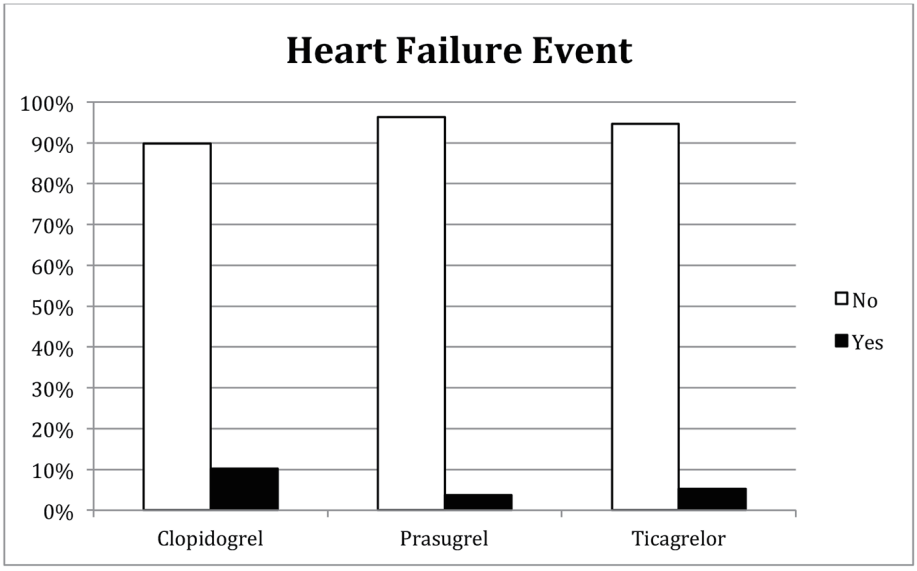

Figure 2. Comparison between antiplatelet drugs for clinical outcome of the heart failure event.

there was a significant association between the type of antiplatelet and the incidence of the composite cardiac outcome (P = 0.049), heart failure (P = 0.002), and bleeding (P = 0.028). Specifically, patients who received prasugrel had a lower incidence than expected for the composite cardiac outcome, heart failure, and bleeding; patients who were administered clopidogrel had a higher incidence of heart failure and bleeding than expected (Table 2, Figs. 1-3).

Discussion

This study compares the safety between the three antiplatelet drugs (i.e. clopidogrel, prasugrel, and ticagrelor) combined with aspirin during hospital stay as they are used in clinical practice. Decisions regarding use of the new antiplatelet drugs are influenced mainly by safety considerations [16-18]. Cost of extended hospital stay due to complications must be taken into account as well.

This study demonstrated that patients treated with prasugrel within 24 h of admission had lower incidence of the clinical composite adverse event, heart failure, and bleeding compared to those treated with clopidogrel and ticagrelor. The presented findings are partly supported by TRITON-TIMI 38 trial, one of the first clinical trials that compared between prasugrel and clopidogrel in ACS patients [12]. The TRITON-TIMI 38 trial showed that both loading and maintenance dose of prasugrel has higher efficacy than clopidogrel [12].

The TRITON-TIMI 38 trial also demonstrated that ACS patients treated with prasugrel had a higher incidence of bleeding on long-term follow-up [12, 19]. However, those reported findings conflict with other studies. For example, previous

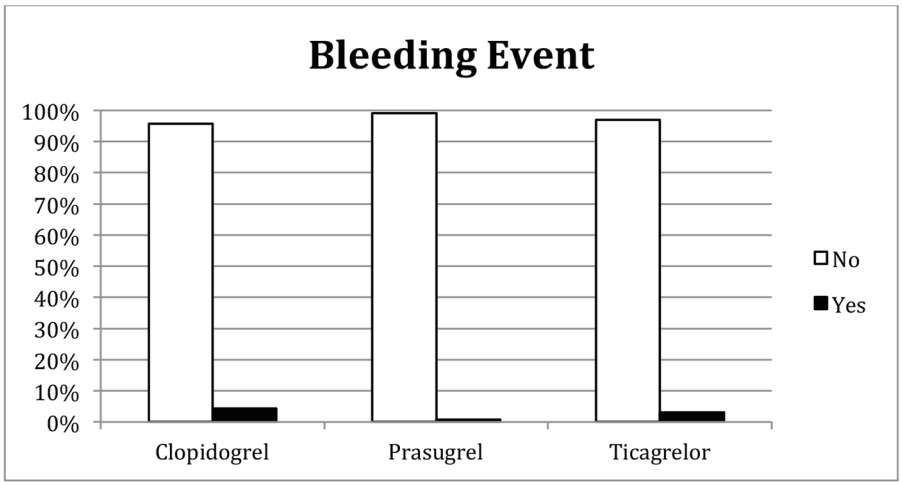

Figure 3. Comparison between antiplatelet drugs for clinical outcome of the bleeding event.

studies concluded that there was no difference in bleeding incidence between prasugrel and clopidogrel [20, 21]. Other studies demonstrated that prasugrel, compared to clopidogrel, had more frequent minor/minimal bleeding events but fewer incidences of major bleeding events [22, 23]. The findings of the presented study determined that patients receiving prasugrel had a lower incidence of in-hospital major bleeding events compared to those administered clopidogrel, agreeing with the latter previous studies with long-term follow-up [22, 23]. The lower incidence of major bleeding among the prasugrel group may be explained by selection bias such that prasugrel is prescribed to patients with a low risk of bleeding [22, 24].

Patients, with ACS, administered prasugrel also had a lower incidence of heart failure than those that were administered clopidogrel. The findings of the presented study agree with those at long-term follow-up for the INFUSE-AMI trial [20].

As with all observational researches, there are inherent limitations in the conclusions to be drawn from this single-center, non-randomized study as it can demonstrate only associations, not causality. A second limitation is that the number of patients who received ticagrelor within 24 h of admission is less than that who received clopidogrel and prasugrel. This difference may be explained, in part, by the fact that ticagrelor was approved more recently than the other antiplatelet agents, which had been commercially available for a longer duration. Future studies can be performed with more data-points for ticagrelor. A third limitation of our study is that it addressed only in-hospital clinical events, as there was no mandated follow-up of patients following discharge. Another limitation is that choice of antithrombotic agent (heparin or bivalirudin), heparin dose, and active clotting times achieved, were not available in our dataset. Finally, access site, provider experience, or access to drug due to insurance and formulary reasons, which may influence medication choice of medications, were not available for this patient population.

Conclusion

In this single-center, registry-based, and observational study, we found a significant association between the choice of antiplatelet therapy and in-hospital clinical outcomes in patients with ACS. When the three types of antiplatelet drugs compared head-to-head, prasugrel was the safest drug with lower incidences of heart failure and bleeding; higher incidences of heart failure and bleeding were found among patients who received clopidogrel. Our study may assist prescribers in clinical decision-making.

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