

# “Real-World” Comparison of Prasugrel With Ticagrelor in Patients With Acute Coronary Syndrome Treated With Percutaneous Coronary Intervention in the United States

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**Objectives:** The 30-day clinical outcomes with prasugrel or ticagrelor were compared using a US payer database in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). **Background:** Prasugrel and ticagrelor demonstrated superior efficacy with increased non-coronary artery bypass graft major bleeding compared with clopidogrel in randomized clinical trials. No direct randomized or observational studies have compared clinical outcomes between prasugrel and ticagrelor. **Methods:** Patients hospitalized for ACS-PCI between August 1, 2011 and April 30, 2013 and prescribed prasugrel or ticagrelor were selected. Drug treatment cohorts were propensity matched based upon demographic and clinical characteristics. The primary objective compared 30-day net adverse clinical events (NACE) in prasugrel- and ticagrelor-treated patients using a prespecified 20% noninferiority margin. Secondary objectives included comparisons of major adverse cardiovascular events (MACE) and major bleeding. **Results:** Data were available for 16,098 patients (prasugrel,  $n = 13,134$ ; ticagrelor,  $n = 2,964$ ). In unmatched cohorts, prasugrel-treated patients were younger with fewer comorbidities than ticagrelor-treated patients, and 30-day NACE rates were 5.6 and 9.3%, respectively ( $P < 0.001$ ). Following propensity matching, NACE was noninferior ( $P < 0.001$ ) and 22% lower in prasugrel-treated than in ticagrelor-treated patients (RR, 0.78; 95% CI, 0.64–0.94). A 30-day adjusted MACE (RR, 0.80; 95% CI, 0.64–0.98) and major bleeding (RR, 0.65; 95% CI, 0.45–0.95) were also lower in prasugrel-treated patients compared with ticagrelor-treated patients. **Conclusions:** In this “real-world,” retrospective, observational study, physicians appear to preferentially use prasugrel in younger patients with lower risk of bleeding or comorbidities compared with ticagrelor. Following adjustment, clinical outcomes associated with prasugrel use appear as good, if not better, than those associated with ticagrelor in ACS-PCI patients. © 2015 Wiley Periodicals, Inc.

**Key words:** myocardial infarction; major bleeding; observational study; antiplatelet

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## INTRODUCTION

About 1.1 million people in the US are diagnosed every year with acute coronary syndrome (ACS) [1]. Current treatment guidelines for patients with ACS undergoing percutaneous coronary intervention (PCI) recommend dual antiplatelet therapy (DAPT), a combination of aspirin and a P2Y<sub>12</sub> inhibitor, for at least 12 months after the ACS event [2–5]. Clopidogrel remains the most widely used P2Y<sub>12</sub> inhibitor. Incremental benefit compared with clopidogrel has been shown with the more potent P2Y<sub>12</sub> inhibitors, prasugrel and ticagrelor, although at the risk of increased noncoronary artery bypass graft (CABG)-related major bleeding [6,7]. Guidelines of the American Heart Association/American College of Cardiology (AHA/ACC) and the European Society of Cardiology (ESC) for patients with non-ST-elevation (NSTEMI)-ACS and ST-elevation myocardial infarction (STEMI) recommend the use of ticagrelor or prasugrel over clopidogrel for patients with ACS undergoing PCI who can take these drugs safely [2–5].

To date, there are no randomized clinical trial data directly comparing the safety and efficacy of prasugrel with ticagrelor. Indirect comparisons have shown no significant efficacy differences between the two drugs, with the exception that prasugrel may be better at reducing stent thrombosis, and no apparent difference in major non-CABG related bleeding [8–10]. However, these indirect comparisons are complicated by differences in trial design and study populations in the studies reviewed, including differential use of an invasive management strategy, clopidogrel loading dose regimens, timing of study drug initiation, duration of therapy, endpoint definitions, and geographic variation in patient recruitment.

It is also unknown how the more potent antiplatelet therapies, prasugrel and ticagrelor, compare with each other in real-world effectiveness and safety. Therefore, the aim of this retrospective observational analysis was to compare the effectiveness and safety of prasugrel and ticagrelor in routine clinical practice using a large US hospital charge master database.

## MATERIALS AND METHODS

### Study Design and Data Source

A retrospective cohort study of patients hospitalized for ACS managed with PCI and prescribed prasugrel or ticagrelor was conducted using the IMS Health Hospital Charge Data Master (CDM). The CDM records are drawn from hospital operational files and other reference sources from over 650 hospitals, covering 7 million inpatient stays and 60 million outpatient visits annually. Data elements include all inpatient and outpatient encounters within a facili-

ty, linked to individual departments, with detailed drug, procedure, diagnosis, and associated charge data. Within the CDM, 213 hospitals contributed data for the current study. Data on mortality was accessed via a linkage to the Social Security Death Index (SSDI). In compliance with the Health Insurance Portability and Accountability Act (HIPAA), patient data included in the analysis were deidentified and, therefore, informed consent could not be obtained. Additionally, because these data were deidentified and analyses of the data were retrospective, observational, and noninterventional in nature, institutional review board (IRB) review was deemed unnecessary.

Patients were placed into one of two drug treatment cohorts for analysis: those prescribed prasugrel and those prescribed ticagrelor during the index ACS-PCI hospitalization. Follow-up periods from the index hospital admission through 30- and 90-days post discharge allowed for assessment of clinical outcomes.

### Patient Population

The study identified adult patients (aged  $\geq 18$  years of age) who had an index hospital admission and discharge between August 1, 2011, and April 30, 2013, with a primary or secondary diagnosis of ACS, managed with PCI, and treated with prasugrel or ticagrelor. This ACS-PCI population was the primary population for the study. ACS diagnosis was determined using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, and PCI was identified by ICD-9-CM and Current Procedural Terminology (CPT-4) procedure codes. Patients with evidence (billing code) of a stent without a corresponding PCI procedure code were not included in the sample. At least one hospital claim for either prasugrel or ticagrelor during the index ACS-PCI hospitalization was required for inclusion in the study sample; patients with claims for both prasugrel and ticagrelor were excluded. The selection of patients for analysis in this study, according to these inclusion and exclusion criteria, is presented in Fig. 1.

Two major subgroups for analysis were defined using criteria guided by the prasugrel (Effient<sup>®</sup>) US prescribing information (USPI) as applied to all patients in the study, regardless of drug treatment cohort [11]. The Label subgroup excluded patients with a history of transient ischemic attack (TIA) or stroke, as these patients are contraindicated for treatment with prasugrel [11]. The Core subgroup excluded patients with a history of TIA or stroke, and was further limited by excluding patients who were  $\geq 75$  years of age with no diabetes mellitus (DM) or prior MI, as prasugrel is generally not recommended for these patients [11,12] (Fig. 1), although these restrictions do not apply to ticagrelor.

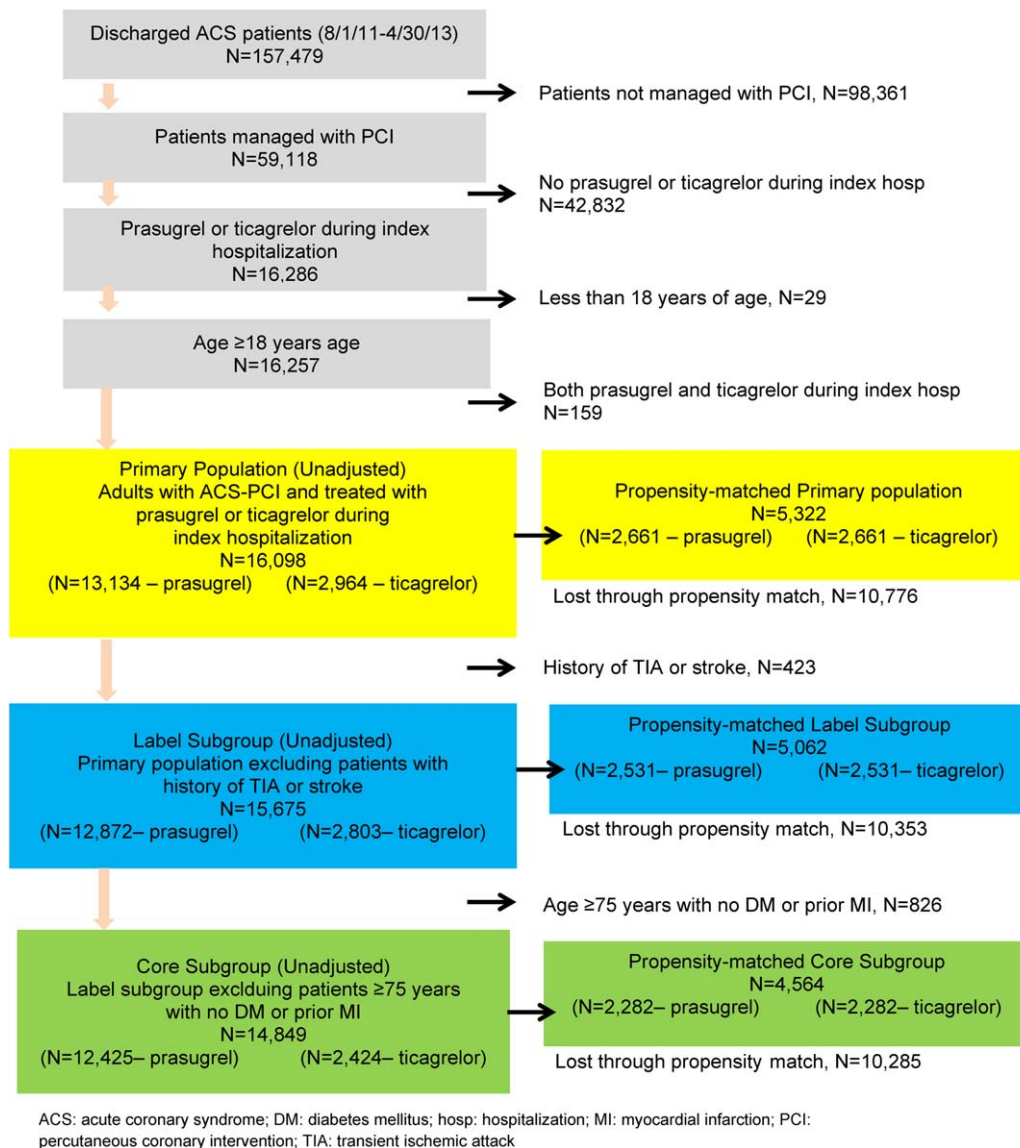


Fig. 1. Study population attrition. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

Baseline information included demographic data, preindex healthcare resource utilization, and comorbidities (e.g., anemia, DM, chronic kidney disease, heart failure, and hypertension) identified via diagnosis-related data from hospitalization records. The baseline period began at index ACS hospital admission and extended back to January 1, 2008, where available, in order to capture a comprehensive co-morbidity profile. Data from the index hospitalization were also used to identify selected baseline comorbidities such as DM or peripheral vascular disease, as these conditions were considered to be pre-existing even if not documented in preindex records. A Charlson Comorbidity Index score was calculated for each patient from this compiled ICD-9-CM coded comorbidity data [13].

The type of ACS (unstable angina [UA], non-ST-elevation myocardial infarction [NSTEMI], or STEMI) diagnosed at index hospitalization was available for analysis, as were in-hospital treatment patterns, including number of vessels treated during the PCI procedure, number of stents implanted, stent type (bare metal stent [BMS] or drug-eluting stent [DES]), and antithrombotic drug use (e.g., heparin, bivalirudin, clopidogrel) (Tables I and II).

## Endpoints

The primary outcome measure was net adverse clinical events (NACE), defined as the composite of major adverse cardiovascular events (MACE) or major

TABLE I. Baseline Characteristics, Primary Population

Variable	Unmatched			Matched		
	Prasugrel; N = 13,134	Ticagrelor; N = 2,964	P value	Prasugrel; N = 2,661	Ticagrelor; N = 2,661	P value
Age, years (mean ± SD)	58.6 ± 10.8	64.1 ± 12.4	<0.001	62.5 ± 11.5	62.4 ± 11.7	0.761
Female gender (%)	26.7	33.4	<0.001	32.4	32.0	0.792
Hospital type (%)			<0.001			0.833
Teaching	42.6	54.2		54.1	53.9	
Non-teaching	46.5	38.3		39.4	39.2	
Index ACS event (%)			<0.001			0.707
STEMI	38.6	39.6	0.313	40.6	39.3	0.327
NSTEMI	36.4	37.2	0.471	35.9	36.9	0.425
UA	21.6	18.5	<0.001	19.0	18.9	0.916
Unspecified ACS	3.4	4.8	NE	4.5	4.9	NE
Prior history/comorbidities (%)						
Anemia	8.9	13.0	<0.001	11.4	12.1	0.443
Cerebrovascular disease	4.8	9.7	<0.001	8.2	8.3	0.842
CHF	6.9	10.2	<0.001	9.4	9.6	0.852
CKD	8.4	12.9	<0.001	10.8	11.7	0.259
COPD	12.9	15.8	<0.001	16.7	15.3	0.156
Diabetes	37.3	35.9	0.149	35.5	35.9	0.775
Dyslipidemia	77.9	74.3	<0.001	74.3	74.4	0.950
Dyspnea	8.3	10.5	<0.001	9.9	10.1	0.749
Hypertension	35.4	41.1	<0.001	39.2	39.6	0.736
Ischemic heart disease	26.2	30.0	<0.001	28.5	28.6	0.952
Peripheral vascular disease	11.4	16.3	<0.001	14.9	14.7	0.787
Prior CABG	1.5	1.6	0.700	1.8	1.8	1.00
Prior MI	7.7	8.4	0.220	8.3	8.1	0.727
Prior PCI	10.2	10.0	0.666	10.0	9.8	0.819
Prior TIA or stroke	2.0	5.4	<0.001	4.2	4.6	0.547
Pre-Index medication use (%)						
ACE inhibitor	15.6	19.0	<0.001	17.7	18.4	0.545
ADP receptor inhibitor	16.0	17.7	0.023	17.2	17.0	0.856
Diabetes medication	12.2	15.1	<0.001	13.8	14.3	0.608
CCI score (mean)	1.4	1.7	<0.001	1.6	1.7	0.703

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ADP = adenosine diphosphate; CABG = coronary artery bypass grafting; CCI = Charlson comorbidity index; CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; NE = not evaluated; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; TIA = transient ischemic attack; UA = unstable angina.

bleeding. MACE was defined as the composite of all-cause mortality or any cardiovascular (CV) event. Using primary ICD-9-CM diagnosis and/or CPT-4 procedure codes, any CV event was defined as the composite of TIA or stroke, or rehospitalization for MI, UA, congestive heart failure (CHF), revascularization (PCI or CABG), or stent thrombosis. Major bleeding included severe bleeding (defined as the presence of bleeding ICD-9-CM codes and  $\geq 3$  transfusions; no bleeding diagnosis code and  $\geq 4$  transfusions within 2 days; intracranial hemorrhage; or blood transfusions followed by death for any reason within 72 hr) during the index hospitalization and bleeding-related rehospitalization (defined as hospital readmission with the presence of either bleeding ICD-9-CM codes or transfusion). The primary objective of the study was to show that outcomes associated with prasugrel were noninferior to outcomes associated with ticagrelor in ACS-PCI patients.

## Sample Size

Sample-size power calculations assumed a base rate of 6% for NACE through 30 days and a 20% noninferiority margin (defined by the upper limit of the 95% confidence interval [CI] for the point estimate of the relative risk [prasugrel to ticagrelor] not to exceed 1.2, using a one-sided  $\alpha$  level of 0.05 [95% one-sided CI]). Based on these assumptions, it was estimated that the sample size of prasugrel- and ticagrelor-treated patients available in the database would provide at least 80% power to detect noninferiority in the comparison of clinical outcomes in both the primary and label populations.

## Statistical Analysis

Baseline characteristics were analyzed using Chi-square for categorical and *t* test for continuous variables. To control for selection bias between the two

treatments, a 1:1 propensity score matching procedure was used to select two comparable patient populations with similar characteristics [14–16]. Baseline demographics, comorbidities, medication use, and healthcare resource utilization, as well as ACS diagnosis at index hospitalization, were included in the propensity score model (Supporting Information Appendix, Table I). Propensity matching as well as primary and secondary analyses were performed in the primary population and in the label and core subgroups.

For the propensity-matched cohorts, McNemar’s test was used for the primary outcome and all other binary outcomes. Relative risk (RR) was estimated and its 95% CI was constructed. The *P* value for noninferiority testing (*p*-ni) was computed by comparing the mean from a normal distribution of log (RR) with log (1.2), the predefined 20% noninferiority margin. The *P* value for two-sided tests comparing RR with unity (*p*) was also provided.

Time points for evaluation included the aggregate periods of index hospitalization through 30- and 90-days, as well as the 30- and 90-day periods following discharge from the index hospital stay. The denominator for all analyses was constant and assumed no loss of patients during follow-up in these calculations.

Data are presented before and after propensity matching, and a *P*-value <0.05 was considered statistically significant. All statistical analyses were conducted by IMS using SAS version 9.2 (SAS Institute, Cary, NC).

## RESULTS

The database contained 157,479 adult patients hospitalized and discharged with a primary or secondary discharge diagnosis code for ACS. Sixty-three percent (63%) of these patients did not have evidence of a PCI during the hospitalization. Within the population of ACS-PCI patients, 72% did not have evidence of receiving prasugrel or ticagrelor during their inpatient stay. After excluding patients with evidence of both prasugrel and ticagrelor during the same index hospitalization, as well as patients <18 years of age, the study population ultimately included 16,098 patients (prasugrel, *n* = 13,134; ticagrelor, *n* = 2,964) in the unmatched primary population. Following propensity matching, there were 5,322 patients treated with prasugrel or ticagrelor included in the matched primary population (prasugrel, *n* = 2,661; ticagrelor, *n* = 2,661) (Fig. 1).

### Patient Characteristics

Key patient baseline demographic and clinical characteristics for the primary population are summarized in Tables I and II. In the unmatched population, compared with prasugrel-treated patients, ticagrelor-treated

patients were older and were more likely to be female, have evidence of ischemic or bleeding risk factors, or be treated at a teaching hospital. There was a higher frequency of UA as the index ACS diagnosis in prasugrel-treated patients, compared with ticagrelor-treated patients, while the type of MI (STEMI or NSTEMI) did not differ between the two drug treatment cohorts. There was no difference in the proportion of patients with a prior history of MI, prior coronary revascularization, or DM. During the preindex baseline period, ticagrelor-treated patients had higher use of ADP receptor inhibitors, ACE inhibitors, and DM medications, compared with patients treated with prasugrel.

Procedural characteristics of the PCI during the index hospitalization were similar between the 2 drug treatment cohorts, including single-vessel versus multiple-vessel PCI, number of stents placed, and stent type (DES or BMS). Approximately 75% of patients in each treatment cohort received a DES, although specific brands of stents were not routinely captured in the database. Patients treated with prasugrel were more likely to have received a glycoprotein (GP) IIb/IIIa inhibitor, while patients treated with ticagrelor were more likely to have received clopidogrel or bivalirudin, during the index hospitalization (Table II).

Demographic, clinical, and procedural characteristics for the Label and Core subgroups were similar to those observed in the primary population (Supporting Information Appendix, Tables IIa, IIb, IIIa, IIIb). After propensity matching, there were no significant differences in baseline characteristics between prasugrel- and ticagrelor-treated patients in the primary population or in the label, and core subgroups (Table I, Supporting Information Appendix Tables IIa, IIb).

### NACE

Patients in the primary population treated with prasugrel during their index hospitalization were found to have a significantly lower unadjusted NACE rate through 30 days post-discharge, compared with patients treated with ticagrelor (5.6% vs. 9.3%; *P* < 0.001) (Table III). After propensity matching, the comparison between the two cohorts demonstrated a 22% lower RR of NACE in prasugrel-treated patients through 30 days (6.5% vs. 8.4%; RR 0.78; 95% CI 0.64–0.94) compared with ticagrelor-treated patients. This difference not only met the prespecified noninferiority analysis (*p*-ni <0.001), but the event rate in prasugrel-treated patients was significantly lower than the event rate in ticagrelor-treated patients using two-sided testing (*P* = 0.009) (Table III and Fig. 2a).

Consistent with the 30-day results, the unadjusted rate of NACE at 90 days in the unmatched primary population was significantly lower for patients treated

**TABLE II. Index Hospital Treatment Patterns, Unmatched Primary Population**

Variable, n (%)	Prasugrel; N = 13,134	Ticagrelor; N = 2,964	P value
Number of vessels treated			0.618
Single vessel PCI	71.5	70.2	
Multiple vessel PCI	17.2	18.4	
Missing information	11.3	11.4	
Number of stents implanted			0.285
One stent	61.8	62.9	
Multiple stents	33.8	32.1	
Missing information	4.5	5.0	
Stent type			
Bare metal stent	17.7	18.9	0.113
Drug-eluting stent	77.5	76.0	0.069
Unknown	4.9	5.2	0.474
No stent implanted	4.5	5.0	0.246
CABG surgery	0.4	0.5	0.821
Pacemaker	0.8	0.9	0.289
Concomitant			
antithrombotic therapy			
Clopidogrel	28.5	33.6	<0.001
Fibrinolytic therapy	0.9	1.0	0.614
Glycoprotein IIb/IIIa inhibitor	40.7	30.1	<0.001
Unfractionated heparin	87.3	89.0	0.013
Low molecular weight heparin	26.4	27.3	0.328
Bivalirudin	58.6	66.5	<0.001

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

with prasugrel, compared with those treated with ticagrelor. Following matching, the NACE rate at 90 days with prasugrel was noninferior compared with the rate for ticagrelor (10.9% vs. 12.5%; RR 0.88; 95% CI 0.76–1.02;  $p$ -ni <0.001), but while the difference in NACE between the cohorts persisted at 90 days, it was no longer significant ( $P = 0.085$ ) (Table III).

Similar findings were observed in the matched and unmatched label and core subgroups at both 30 and 90 days (Supporting Information Appendix Tables IVa, IVb; Fig. 2a). However, after matching, the reduction in NACE associated with prasugrel treatment at 90 days was statistically significant in these two subgroups (Supporting Information Appendix Tables IVa, IVb).

## MACE

When the components of NACE were assessed separately, significantly lower rates of MACE were observed at 30 days in prasugrel-treated patients in the unmatched primary population, compared with those treated with ticagrelor (4.5% vs. 7.5%;  $P < 0.001$ ). This difference persisted after propensity matching (Table III, Fig. 2b). Similar results were demonstrated in both the label and core subgroups (Fig. 2b; Supporting Information Appendix Tables IVa, IVb).

Consistent with the 30-day results, the rate of MACE at 90 days in the unmatched primary population was signifi-

cantly lower for patients treated with prasugrel, compared with those treated with ticagrelor. Following matching, MACE at 90 days with prasugrel was noninferior to ticagrelor (8.9% vs. 10.0%;  $p$ -ni <0.001), but the difference was not significant ( $P = 0.149$ ) (Table III). Similar results were demonstrated in the both the label and core subgroups (Supporting Information Appendix Tables IVa, IVb).

## Component Endpoints of MACE

**Mortality.** As with the MACE results, unadjusted all-cause mortality in prasugrel-treated patients was significantly lower than in ticagrelor-treated patients in the primary population and in the label, and core subgroups at both 30 and 90 days (Table III, Supporting Information Appendix Tables IVa, IVb). After matching, all-cause mortality rates associated with prasugrel were lower than those associated with ticagrelor, although the differences were no longer significant. However, criteria for noninferiority in relation to the occurrence of fatal events were met (Table III, Supporting Information Appendix Tables IVa, IVb).

**Any CV event.** In the unmatched populations, rates of any CV event in prasugrel-treated patients were significantly lower than in ticagrelor-treated patients at both 30 and 90 days with the largest reduction related to the rate of MI (Table III, Supporting Information Appendix Tables IVa, IVb). After propensity matching, the rate of any CV event associated with prasugrel remained numerically lower than those associated with ticagrelor, and criteria for noninferiority were met at each time point (Table III, Supplemental Appendix Tables IVa, IVb).

**Major bleeding.** Prior to matching, there were significantly fewer bleeding events in prasugrel-treated patients than in ticagrelor-treated patients in the primary population at 30 days (1.7% vs. 2.8%;  $P < 0.001$ ). After propensity matching for baseline patient differences, bleeding events associated with prasugrel met the noninferiority criteria compared with bleeding events associated ticagrelor. The lower bleeding event rate associated with prasugrel was also statistically significant ( $P = 0.026$ ). At 90 days, following propensity matching, the primary population showed no significant difference in bleeding rates, while criteria for noninferiority between the outcomes in the two treatment cohorts were met (Table III). Similar directionality was demonstrated in the label and core subgroups (Fig. 2c; Supplemental Appendix Tables IVa, IVb).

## DISCUSSION

The present observational study provides the first comparative effectiveness and safety evaluation between prasugrel and ticagrelor, as they are used in the “real world” as determined by physician practice. In this study, baseline characteristics of patients treated with prasugrel

TABLE III. Clinical Events Through 30 and 90 Days, Primary Population

	Unmatched			Matched				
	Pras; N = 13,134	Ticag; N = 2,964	P value	Pras; N = 2,661	Ticag; N = 2,661	RR; (95% CI) <sup>a</sup>	P value	P-NI
30-Day Events (%)								
NACE	5.6	9.3	<0.001	6.5	8.4	0.78 (0.64–0.94)	0.009	<0.001
MACE	4.5	7.5	<0.001	5.4	6.8	0.80 (0.64–0.98)	0.033	<0.001
Mortality	1.6	3.0	<0.001	2.1	2.5	0.85 (0.60–1.21)	0.361	0.027
Any CV event	3.0	4.7	<0.001	3.4	4.4	0.77 (0.59–1.00)	0.044	<0.001
MI	0.5	1.2	<0.001	0.5	1.2	0.39 (0.21–0.75)	0.003	<0.001
Revasc	1.8	2.3	0.048	1.9	2.4	0.78 (0.54–1.13)	0.186	0.011
CHF	0.7	1.5	<0.001	1.1	1.4	0.78 (0.48–1.27)	0.317	0.042
UA	0.1	0.2	0.221	0.1	0.2	0.50 (0.09–2.73)	0.414	0.156
ST	0.2	0.5	0.003	0.2	0.5	0.33 (0.11–1.03)	0.046	0.013
TIA	0.1	0	0.601	0.1	0	NE	NE	NE
Stroke	0.1	0.3	0.010	0.1	0.2	0.50 (0.09–2.73)	0.414	0.156
Bleeding	1.7	2.8	<0.001	1.6	2.5	0.65 (0.45–0.95)	0.026	<0.001
Severe bleed	0.3	0.7	0.003	0.3	0.7	0.47 (0.22–1.05)	0.059	0.011
Rehosp	1.4	2.2	0.004	1.3	1.8	0.73 (0.47–1.12)	0.154	0.012
90-day events (%)								
NACE	9.0	13.4	<0.001	10.9	12.5	0.88 (0.76–1.02)	0.085	<0.001
MACE	7.2	10.7	<0.001	8.9	10.0	0.88 (0.75–1.04)	0.149	<0.001
Mortality	1.8	3.5	<0.001	2.5	2.9	0.87 (0.63–1.20)	0.398	0.026
Any CV event	5.5	7.7	<0.001	6.7	7.5	0.90 (0.73–1.08)	0.240	0.001
MI	1.2	2.1	<0.001	1.2	2.2	0.53 (0.34–0.81)	0.003	<0.001
Revasc	3.5	4.2	0.073	3.8	4.3	0.89 (0.69–1.16)	0.408	0.014
CHF	1.2	2.3	<0.001	1.9	2.2	0.88 (0.61–1.28)	0.499	0.051
UA	0.1	0.2	0.791	0.2	0.2	1.00 (0.25–3.99)	1.00	0.398
ST	0.3	0.7	0.006	0.4	0.7	0.56 (0.26–1.20)	0.131	0.025
TIA	0.1	0	0.700	0.2	0	NE	NE	NE
Stroke	0.2	0.3	0.101	0.2	0.2	0.80 (0.22–2.98)	0.739	0.273
Bleeding	2.9	4.4	<0.001	3.4	4.0	0.84 (0.64–1.11)	0.221	0.006
Severe bleed	0.6	1.2	<0.001	0.6	1.2	0.48 (0.26–0.89)	0.018	0.002
Rehosp	2.6	3.8	<0.001	3.1	3.3	0.93 (0.70–1.25)	0.645	0.047

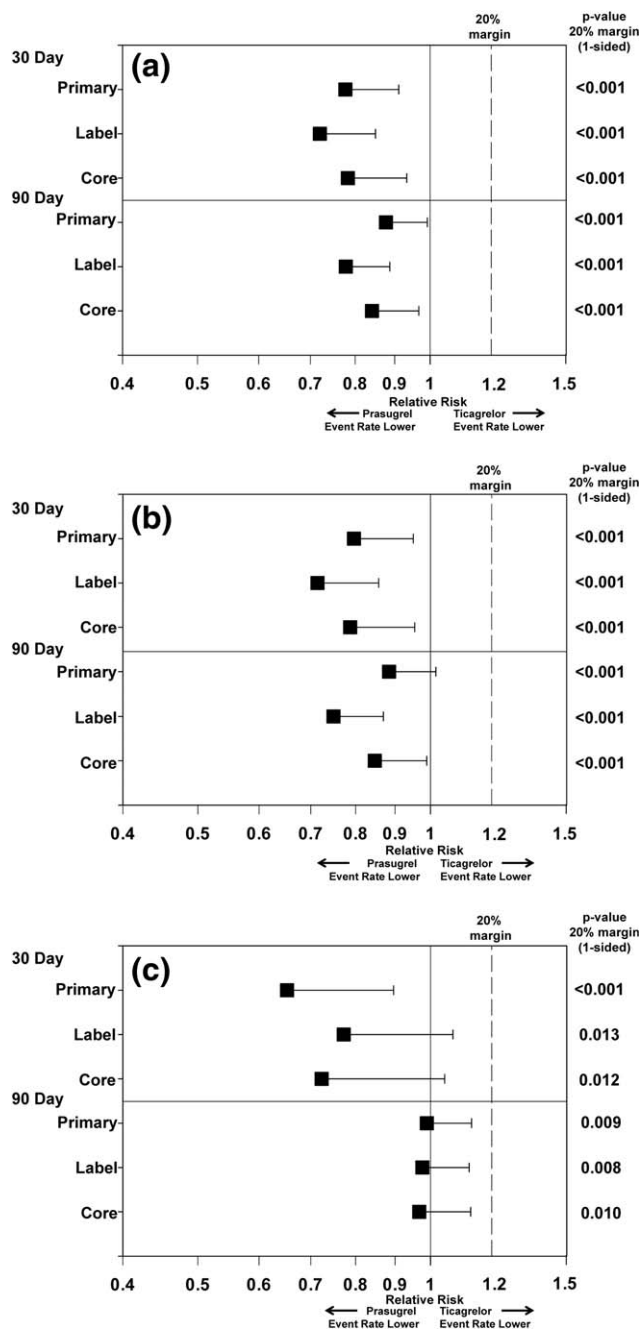
<sup>a</sup>95% CI represents two-sided analysis.

CHF = congestive heart failure; CV = cardiovascular; MACE = major adverse cardiovascular events; MI = myocardial infarction; NACE = net adverse clinical events; NE = not evaluated (too few events); NI = non-inferiority; Pras = prasugrel; Rehosp = rehospitalization; Revasc = revascularization; RR = relative risk; ST = stent thrombosis; TIA = transient ischemic attack; Ticag = ticagrelor; UA = unstable angina.

were significantly different from patients treated with ticagrelor before propensity matching. Ticagrelor-treated patients were older, more often female, and more likely to have chronic comorbidities, including risk factors for bleeding, such as renal impairment, anemia, and heart failure. This differential use of prasugrel compared with ticagrelor in routine clinical practice suggests that physicians do not view these agents as interchangeable. Decisions regarding use of these two antiplatelet drugs may be influenced by safety considerations as noted in publications [8,10] and product labels [11,17]. For example, while both drugs are contraindicated in patients with active pathological bleeding, prasugrel is contraindicated in patients with a prior TIA or stroke [11]. The differences in baseline characteristics were somewhat unexpected, as the drugs do not greatly differ from each other in terms of platelet inhibition. With the current approved maintenance dosing for both drugs, adequate levels of platelet inhibition [18] are achieved in over 90% of patients [11,17,19–22].

Despite the differences in patient baseline characteristics between the treatment cohorts, PCI characteristics (number and type of stent or number of vessels treated) were fairly balanced between the prasugrel- and ticagrelor-treated cohorts, which may suggest consistency in healthcare delivery to the overall ACS-PCI population, irrespective of antiplatelet agent selection or baseline clinical characteristics.

In line with the baseline differences in patient populations prescribed prasugrel compared with ticagrelor, results in unmatched cohorts showed significantly lower ischemic and bleeding outcomes associated with prasugrel compared with ticagrelor at 30 and 90 days after the index hospital discharge. After propensity matching, NACE, MACE, mortality, and major bleeding rates associated with prasugrel were noninferior to rates associated with ticagrelor, meeting the primary objective of the study. Additionally, compared with ticagrelor, prasugrel was associated with significantly lower 30-day NACE and MACE, compared to ticagrelor. At 90 days, the difference in



**Fig. 2.** (a) 30- and 90-day matched comparisons: NACE. (b) 30- and 90-day matched comparisons: MACE. (c) 30-day matched comparisons: Bleeding.

NACE was no longer significant in the Primary population. The observation of an early effectiveness with prasugrel through 30 days is consistent with that from the TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) trial where the difference between prasugrel and clopidogrel occurred early, an advantage that may lessen over time,

while the benefit with ticagrelor compared with clopidogrel in the PLATelet Inhibition and Patient Outcomes (PLATO) study showed a delay in the separation of event rates [6,7]. The finding that the outcomes in the prasugrel cohort were noninferior to the outcomes in the ticagrelor cohort is consistent with evidence from network meta-analyses [8–10] and plausible from a pharmacodynamics perspective. However, while the finding of significantly lower rates of ischemic events associated with prasugrel is directionally in line with the meta-analyses cited above, the magnitude of the difference was unexpected and needs to be cautiously interpreted in the absence of data from a randomized clinical trial comparing the two drugs. This unexpected difference may be explained by several potential mechanisms. First, while propensity score adjustment has been reported to eliminate > 90% of the treatment bias in observational cohorts, observational studies are still subject to residual and unmeasured confounding bias [14]. Second, although aspirin dose was not captured in this study, the data here may represent outcomes associated with use of high-dose aspirin ( $\geq 300 \text{ mg day}^{-1}$ ) as the PLATO study demonstrated reduced efficacy of ticagrelor with high-dose aspirin [23], an interaction not seen with prasugrel in TRITON-TIMI 38 [24]. Third, while implications of ticagrelor-induced nonplatelet side effects (e.g., dyspnea, ventricular pauses) and of a twice-daily dosing regimen on medication adherence and discontinuation are largely unknown, these factors may confer an increased risk for subsequent cardiac events, especially given the more rapid offset of the antiplatelet effect of ticagrelor. Finally, an actual difference in outcomes or differences due to the combination of these potential mechanisms cannot be discounted.

As with all observational research, there are inherent limitations in the conclusions to be drawn from the data, and the current study can only demonstrate associations, not causality. In this database, event rates may be underestimated because events that occurred at a non-IMS Health CDM hospital site were not available for analysis. While the study included available baseline disease information back to 2008, events prior to this date were not captured. Stent thrombosis events may be underestimated, as a specific ICD-9-CM code for stent thrombosis does not exist. The relevance of including CHF as a component endpoint may be questioned. However, as the difference in periprocedural MI between the more potent ADP receptor inhibitors and clopidogrel was more apparent in TRITON-TIMI 38 [6] than in PLATO [7], in a payer database, the presence of CHF may be an indicator of the severity and extent of the presenting infarction. However, the diagnosis of CHF may also have been a marker of the difference in rates of dyspnea as a side effect of ticagrelor [7]. Additionally, all medical conditions, either at baseline or used to determine outcomes, were derived



from a healthcare administrative database that includes orders from hospital CDM systems with no access to medical charts. Medication switching and adherence to prescribed therapy through the study follow-up period were not assessed, given only hospital CDM records were used without access to outpatient pharmacy data. Likewise, over-the-counter medications, especially aspirin (use or dose), were not available in the database. Despite the use of a propensity-matched cohort, several potential confounders were not available for analysis, including patient socioeconomic status, body mass index, and weight. Similarly, provider experience (e.g., years in practice, case volume, and case selection) or access to drug, (e.g., formulary inclusion) which may influence the choice of medications were not available from this data source. Geographic imbalances existed, with 64% of the study population located in the Southern US. Finally, the ACS-PCI study selection criteria more closely represented the population indicated for prasugrel in the US, as ticagrelor is also indicated for patients with ACS not managed by PCI. Therefore, these results may not be generalizable to other populations.

## CONCLUSION

In this first retrospective observational direct comparison of newer potent ADP receptor inhibitors among ACS-PCI patients, there was differential use of prasugrel compared with ticagrelor in routine clinical practice, suggesting that physicians do not view these agents as interchangeable. Outcomes associated with prasugrel were noninferior to outcomes associated with ticagrelor when 30- and 90-day rates of NACE, MACE, mortality, and bleeding were compared. Additionally, prasugrel was associated with significantly lower 30-day NACE and MACE compared to ticagrelor. These data support the hypothesis that in the “real-world” setting, ticagrelor and prasugrel are generally similar with regard to 30- and 90-day CV or bleeding outcomes in ACS-PCI patients. The unexpected finding of a differential effect of prasugrel compared with ticagrelor needs to be cautiously interpreted, given the limitations of observational studies and the lack of randomized controlled clinical trial evidence between these two drugs. However, observations from this current study may provide important information for prescribers in clinical decision making.

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## **Editorial Comment**

### **ACS Treatment Continues to Improve: But Price Matters**

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#### **Key Points**

- Over 90% of patients achieve adequate levels of platelet inhibition with both Prasugrel and Ticagrelor.
- The introduction of Prasugrel was met with some hesitation from physicians because of the significant increase in cost.
- This pharmaceutically sponsored and authored retrospective study suggests that both agents are effective.

“Be careful with new products”. William Osler. Thayer WS. *The teacher*, in *Osler and other papers*. Baltimore: Johns Hopkins University Press; 1931.

“Cultivate a skeptical attitude toward drugs”. William Osler. *The fate that heals*. *Brit Med J* 1910;1:470-2.

Conflict of interest: Nothing to report.

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