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Ninety-day Readmission and Long-Term Mortality in Medicare Patients (≥ 65 Years) Treated With Ticagrelor Versus Prasugrel After Percutaneous Coronary Intervention (From the Blue Cross Blue Shield of Michigan Cardiovascular Consortium)

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Abstract

Ticagrelor and prasugrel were found to be superior to clopidogrel for the treatment of acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI); however, the comparative effectiveness of these 2 drugs remains unknown. We compared post-discharge

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All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors agree with the manuscript.

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outcomes among older patients treated with ticagrelor versus prasugrel after PCI for ACS. We linked clinical data from PCIs performed in older patients (age ≥ 65) for ACS at 47 Michigan hospitals to Medicare fee-for-service claims from January 1, 2013 through December 31, 2014 to ascertain rates of 90-day readmissions and long-term mortality. We used propensity score matching to adjust for the non-random use of ticagrelor and prasugrel at discharge. Logistic regression and Cox proportional hazards models were used to compare rates of 90-day readmission and long-term mortality, respectively. Patients discharged on ticagrelor (n=1,243) were more frequently older, female, had a history of cerebrovascular disease, and presented with ST- or non-ST-elevation myocardial infarction compared with prasugrel (n=1,014). After matching (n=756 per group), there were no significant differences in the rates of 90-day readmission (16.7% ticagrelor vs 14.6% prasugrel; adjusted OR: 1.15; 95% CI: 0.86–1.55; P=0.35) or 1-year mortality (5.4% ticagrelor vs 3.7% prasugrel; HR 1.3; 95% CI: 0.8–2.2; P=0.31). In conclusion, we found no significant differences in the rates of 90-day readmission or long-term mortality between older patients treated with ticagrelor compared with patients treated with prasugrel after PCI for ACS. In the absence of randomized data on the contrary, these 2 treatments appear similarly effective.

Keywords

Ticagrelor; Prasugrel; PCI; Outcomes

Introduction

Over the past decade, the armamentarium of P2Y₁₂ inhibitors has expanded with the approval of ticagrelor and prasugrel. In randomized controlled trials (RCTs), these medications were found to be superior to clopidogrel among patients treated with percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS).^{1,2} Due to the dearth of research directly comparing the effectiveness of ticagrelor and prasugrel, it remains difficult to make evidence-based decisions regarding the choice of treatment between them. A recent head-to-head RCT comparing clinical endpoints between ticagrelor and prasugrel demonstrated no significant differences in primary or secondary endpoints; however, the trial was terminated early due to futility.³ There is also a paucity of observational research comparing these 2 treatments.^{4,5} Because older patients are at an increased risk of ACS and post-PCI complications,^{6–8} we sought to assess the comparative effectiveness of these two drugs after PCI among Medicare patients aged ≥ 65 years presenting with ACS.

Methods

We performed a retrospective analysis on data collected by the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2), a registry of all patients who underwent PCI in the state of Michigan. This is a prospective, multicenter, statewide registry of patients who underwent PCI at any non-federal hospital in Michigan. A more detailed description of the registry, including data collection and auditing practices, has been described previously.^{9,10} For this study, we evaluated consecutive patients who underwent PCI and were discharged

alive between January 1, 2013, and December 31, 2014, in the 47 hospitals involved in the registry.

To evaluate post-discharge outcomes including 90-day readmission and long-term mortality, we linked clinical data from the BMC2 PCI registry with administrative Medicare claims through indirect matching on multiple variables including admission, discharge, and procedure dates for the index hospitalization; patient gender; date of birth; and hospital and operator NPI numbers. Medicare data were made available through a collaboration with the Michigan Value Collaborative.¹¹

Medicare beneficiaries discharged alive after PCI from January 1, 2013 to December 31, 2014 and assigned a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) at discharge served as the initial study cohort to which inclusions and exclusions were applied. First, we included all patients discharged alive on ticagrelor or prasugrel as documented in the BMC2 PCI clinical registry. Next, we excluded patients aged <65 years, on dialysis before PCI, or discharged to a nursing home, or patients who underwent PCI for a non-ACS presentation. We also excluded those patients who experienced post-procedural complications including stroke, major bleeding, or major surgery, as these clinical complications may significantly influence the choice of P2Y12 inhibitor use.

The primary outcomes included the rate of readmission within 90 days of discharge and long-term mortality. Readmission was defined as readmission to the hospital for any reason within 90 days after discharge from the hospitalization where PCI occurred. Only the first readmission was counted per PCI episode. Finally, the patient's vital status and date of death were determined from each patient's Medicare beneficiary file.

We used propensity score matching to account for the non-random use of ticagrelor and prasugrel. A logistic regression model was used to estimate propensity scores among patients receiving ticagrelor or prasugrel with demographic and clinical variables included as predictors (Supplementary Table S1). Patients receiving ticagrelor were matched in a 1:1 fashion to similar patients receiving prasugrel using a greedy matching algorithm. We required exact matching on the type of PCI including balloon only, bare metal stent, drug-eluting stent, or mixed.

Next, we reported adjusted odds ratios (aOR) for the outcome of 90-day readmission using logistic regression models adjusting for potential confounding variables listed in Supplementary Table S1. We used Kaplan-Meier curves in the matched cohort to depict differences in cumulative mortality between the 2 treatment groups. Cox proportional hazards models adjusting for confounding (variables listed in Supplementary Table S1) were used to estimate the effect of treatment choice on long-term mortality.

In a sensitivity analysis, we excluded patients with relative or absolute contraindications to prasugrel from the derivation cohort. These contraindications included a history of cerebrovascular disease, age >75 years, or weight <60 kg. All primary analyses were repeated in this cohort. Per the NCDR CathPCI registry, cerebrovascular disease was defined as a history of stroke, transient ischemic attack, non-invasive or invasive carotid testing with

>79% occlusion, or previous carotid artery surgery or intervention for carotid artery stenosis.
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Results

Between January 1, 2013, and December 31, 2014, a total of 13,702 Medicare patients undergoing PCI were discharged alive on clopidogrel, ticagrelor, or prasugrel at 47 hospitals in Michigan. Of these, 10,261 were discharged on clopidogrel and were excluded. After further exclusions including those aged <65 years old, there were 1,243 patients in the ticagrelor group and 1,014 patients in the prasugrel group (Figure 1). Baseline characteristics of the unmatched and matched cohorts are presented in Table 1. Finally, after propensity score matching, 756 patients were included in each group. The absolute standardized differences were <10% on all matched variables, suggesting good covariate balance between the 2 groups (Table 1 & Figure 2).

Among the matched cohort, 16.7% (n/N=125/756) and 14.6% (n/N=109/756) of patients treated with ticagrelor and prasugrel, respectively, had at least 1 readmission within 90 days of discharge. There was no significant difference in the risk of 90-day readmission between ticagrelor and prasugrel (aOR 1.15; 95% CI: 0.86–1.55; P=0.35). The 1-year mortality rate for patients discharged on ticagrelor was 5.4% (95% CI: 3.3 – 7.4%) whereas for prasugrel it was 3.7% (95% CI: 2.2 – 5.2%) (Figure 3). There was no significant difference in the hazard rates of mortality between patients treated with ticagrelor compared with prasugrel (HR 1.3; 95% CI: 0.8 – 2.2; P=0.31).

In a sensitivity analysis, we excluded 653 (52.5%) patients treated with ticagrelor and 257 (25.3%) patients treated with prasugrel who had absolute or relative contraindications to prasugrel which included a history of cerebrovascular disease, age >75 years, or weight <60 kg (Supplementary Table S2). This left 590 patients treated with ticagrelor and 757 patients treated with prasugrel available for matching. 486 patients remained in each group. Within this subgroup, there was no significant difference in the rate of 90-day readmission between the 2 treatments (14.4% ticagrelor vs 13.0% prasugrel; aOR 1.14; 95% CI: 0.78 – 1.68; P=0.5). The 1-year mortality rate for ticagrelor and prasugrel were 4.8% (95% CI: 2.4–7.2%) and 2.3% (95% CI: 0.9 – 3.7%), respectively, and the hazard ratio of mortality was 1.6 (95% CI: 0.8 – 3.5; P=0.19) (Figure 4).

Discussion

In this retrospective observational study examining patients discharged on ticagrelor or prasugrel after undergoing PCI for ACS, we found no significant differences in the rates of 90-day readmission and 1-year mortality among matched patients. After excluding patients with absolute or relative contraindications to prasugrel in a sensitivity analysis, we found no significant differences in the rates of readmission or mortality.

There is reason to believe that there may be important differences in the effectiveness of these 2 treatments. Ticagrelor is active in both its parent and metabolite forms, whereas prasugrel is a prodrug that requires CYP450 enzymes to become active.^{13,14} This may factor into important differences in platelet inhibition seen in several in vivo pharmacologic

studies.^{15–17} In addition, given that prasugrel is metabolized by the CYP450 system,¹⁴ active metabolite levels could be affected by common medications or dietary interactions. Also, as stent thrombosis is becoming less common due to advances in stent technologies, pathological bleeding from excessive platelet inhibition may contribute more towards morbidity and mortality among patients taking these drugs.

Indeed, compared with patients treated with clopidogrel, patients with a history of cerebrovascular disease, aged >75 years, or weight of <60 kg treated with prasugrel experienced inferior outcomes in TRITON-TIMI 38.² In our unmatched cohort, 257 (25.3%) patients discharged on prasugrel had these comorbidities. This relatively high rate of patients having a contraindication to prasugrel may partially be explained by the broader definition of cerebrovascular disease used in this study which included patients with carotid artery stenosis (>79% occlusion) or a previous carotid artery surgery or intervention (12). Thus, some patients may have been classified as having a history of cerebrovascular disease without a history of stroke or transient ischemic attack. These patients would not be considered to have true contraindications to prasugrel. Regardless, this finding emphasizes the need to focus quality improvement efforts at using these antiplatelet agents in the appropriate patients.

Beyond pharmacological differences, other factors may play a role in the use of these agents. For instance, ticagrelor's twice daily dosing may impact patient compliance compared with prasugrel's once daily dosing. A meta-analysis explored this concept and found a significantly lower compliance rate in twice daily versus once daily dosing of antihypertensive medications.¹⁸ Beigel et al observed a trend towards lower compliance rate among patients treated with ticagrelor compared with prasugrel.⁵ They also noted crossover rates to a different P2Y₁₂ inhibitor to be higher among patients initially treated with ticagrelor compared with patients treated with prasugrel and attributed this to the inferior side-effect profile of ticagrelor (5). In contrast, the increased risk of bleeding with prasugrel, as demonstrated in TRITON-TIMI 38, may be associated with decreased compliance.²

Finally, costs are an important consideration as studies have shown decreasing medication compliance with increasing out-of-pocket costs.^{19,20} In upcoming years, these drugs will become generic and thus significantly cheaper. The specific time of transition to generic medications remains unclear as both manufacturers have applied for 30-month stays on their patents.^{21,22} However, given the earlier patent expiration date for prasugrel, it will likely become generic sooner than ticagrelor.^{23,24} As such, if there remains a clinical equipoise between the two drugs, prasugrel may be the more cost-effective treatment option.

Although we demonstrated no significant differences in the rates of 90-day readmission and long-term mortality between ticagrelor and prasugrel, RCTs are essential in guiding clinical decision making. An ongoing RCT, ISAR-REACT 5, is currently enrolling patients to evaluate the safety and efficacy of ticagrelor and prasugrel in patients who underwent PCI for ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, or unstable angina.²⁵ This study should provide insights into the comparative efficacy of these 2 drugs. Until RCTs can produce definitive evidence for which drug to use, we need to rely on observational studies such as ours to guide practice.

This study should be interpreted in the context of several limitations. First, although we attempted to account for the non-random administration of ticagrelor and prasugrel through propensity-matching techniques, we were unable to account for all potential confounders due to the observational nature of this study. Second, all hospitals participating in this registry are actively engaged in statewide collaborative quality improvement initiatives. Therefore, these findings may not be generalizable to hospitals that do not participate in such initiatives.²⁶ Third, we studied older Medicare patients in the state of Michigan, thus potentially limiting generalizability. However, elderly patients are at especially high risk of post-discharge complications including readmission and death(6,7); therefore, this is an important population to study and understand the potential adverse outcomes of these treatments. Finally, as previously noted, we could not account for medication compliance, treatment discontinuation, or treatment switching, all of which may have important effects on outcomes and warrants further research.

In this retrospective analysis of ticagrelor and prasugrel treatments in older Medicare patients who underwent PCI for ACS, there were no significant differences in the rates of 90-day hospital readmission or long-term mortality. With prasugrel's potential earlier patent expiration and generic drug approval, it may emerge as a more cost-effective agent compared with ticagrelor in the near future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Study flow diagram.

Abbreviations: PCI= percutaneous coronary intervention

Figure 2.

Plot of absolute standardized differences before and after matching.

Absolute standardized differences before and after matching in PCI patients discharged on ticagrelor and prasugrel.

Abbreviations: CABG = coronary artery bypass grafting; CAD = coronary artery disease; CVD = cerebrovascular disease; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; Sx = symptoms.

Figure 3.

Kaplan-Meier curve for cumulative long-term mortality.

Kaplan-Meier curve demonstrating long-term mortality in propensity-matched patients. The hazard ratio is presented in the upper left corner.

Abbreviations: CI = confidence interval

Figure 4.

Kaplan-Meier curve for cumulative long-term mortality after exclusion of patients with contraindications to prasugrel.

Kaplan-Meier curve demonstrates long-term mortality in a sensitivity analysis excluding patients with a history of cerebrovascular disease, age >75 years, weight <60 kg. The hazard ratio is presented in the upper left corner.

Abbreviations: CI = confidence interval

Table 1

Baseline characteristics of the unmatched and matched cohorts

Variable	Before Matching			After Matching		
	Prasugrel (n=1,014)	Ticagrelor (n=1,243)	p-value	Prasugrel (n=756)	Ticagrelor (n=756)	p-value
Age (Years)	70.96 ± 4.64	74.50 ± 6.54	< 0.001	71.73 ± 4.83	71.80 ± 5.07	0.783
Women	328/1,014 (32.3%)	517/1,243 (41.6%)	< 0.001	262/756 (34.7%)	268/756 (35.4%)	0.746
Body Mass Index (kg/m ²)	30.39 ± 6.29	29.49 ± 7.14	0.001	30.19 ± 6.27	30.20 ± 6.12	0.991
White	936/1,014 (92.3%)	1,143/1,243 (92.0%)	0.757	695/756 (91.9%)	693/756 (91.7%)	0.851
Black	59/1,014 (5.8%)	74/1,243 (6.0%)	0.892	45/756 (6.0%)	45/756 (6.0%)	1.000
Current/Recent Smoker	180/1,014 (17.8%)	170/1,243 (13.7%)	0.008	125/756 (16.5%)	125/756 (16.5%)	1.000
Hypertension	877/1,014 (86.5%)	1,086/1,242 (87.4%)	0.504	658/756 (87.0%)	655/756 (86.6%)	0.820
Dyslipidemia *	840/1,014 (82.8%)	993/1,242 (80.0%)	0.080	618/756 (81.7%)	621/756 (82.1%)	0.841
Family History of Premature Coronary Artery Disease	138/1,014 (13.6%)	126/1,241 (10.2%)	0.011	93/756 (12.3%)	95/756 (12.6%)	0.876
Prior Myocardial Infarction	298/1,014 (29.4%)	314/1,243 (25.3%)	0.028	206/756 (27.2%)	213/756 (28.2%)	0.688
Prior Heart Failure	114/1,014 (11.2%)	163/1,241 (13.1%)	0.173	85/756 (11.2%)	90/756 (11.9%)	0.688
Prior Valve Surgery/Procedure	11/1,014 (1.1%)	16/1,242 (1.3%)	0.658	<11	11/756 (1.5%)	0.489
Prior Percutaneous Coronary Intervention	458/1,014 (45.2%)	442/1,242 (35.6%)	< 0.001	309/756 (40.9%)	306/756 (40.5%)	0.875
Cerebrovascular Disease	99/1,014 (9.8%)	202/1,243 (16.3%)	< 0.001	88/756 (11.6%)	85/756 (11.2%)	0.808
Peripheral Arterial Disease	143/1,014 (14.1%)	166/1,243 (13.4%)	0.607	112/756 (14.8%)	116/756 (15.3%)	0.774
Chronic Lung Disease	203/1,013 (20.0%)	237/1,243 (19.1%)	0.562	157/756 (20.8%)	156/756 (20.6%)	0.949
Diabetes Mellitus	402/1,014 (39.6%)	446/1,243 (35.9%)	0.066	290/756 (38.4%)	295/756 (39.0%)	0.792
Heart Failure within 2 Weeks	88/1,014 (8.7%)	101/1,242 (8.1%)	0.641	54/756 (7.1%)	67/756 (8.9%)	0.218
Left Ventricular Systolic Dysfunction	80/1,014 (7.9%)	77/1,243 (6.2%)	0.115	56/756 (7.4%)	52/756 (6.9%)	0.690
Cardiogenic Shock within 24 Hours	<11	17/1,243 (1.4%)	0.288	<11	<11	0.795
Cardiac Arrest within 24 Hours	<11	19/1,243 (1.5%)	0.171	<11	<11	1.000
Pre-Procedure Creatinine (mg/dL)	1.04 ± 0.33	1.06 ± 0.36	0.352	1.04 ± 0.33	1.04 ± 0.38	0.633
Pre-Procedure Hemoglobin (g/dL)	13.62 ± 1.64	13.45 ± 1.73	0.015	13.65 ± 1.65	13.64 ± 1.69	0.889
CAD presentation						
Unstable angina pectoris	619/1,014 (61.0%)	614/1,243 (49.4%)	< 0.001	436/756 (57.7%)	435/756 (57.5%)	0.959
Non-ST-Elevation Myocardial Infarction	233/1,014 (23.0%)	358/1,243 (28.8%)	0.002	191/756 (25.3%)	201/756 (26.6%)	0.557
ST-Elevation Myocardial Infarction	162/1,014 (16.0%)	271/1,243 (21.8%)	< 0.001	129/756 (17.1%)	120/756 (15.9%)	0.533

Variable	Before Matching		After Matching	
	Prasugrel (n=1,014)	Ticagrelor (n=1,243)	Prasugrel (n=756)	Ticagrelor (n=756)
<i>Procedural characteristics</i>				
Intra-Aortic Balloon Pump	11/1,014 (1.1%)	21/1,242 (1.7%)	<11	11/755 (1.5%)
Other Mechanical Ventricular Support	<11	<11	<11	<11
Arterial Access Site: Femoral	778/1,014 (76.7%)	876/1,243 (70.5%)	560/756 (74.1%)	551/756 (72.9%)
Arterial Access Site: Radial	233/1,014 (23.0%)	364/1,243 (29.3%)	193/756 (25.5%)	204/756 (27.0%)
Balloon only	16/1,014 (1.7%)	28/1,243 (2.8%)	11/756 (1.5%)	11/755 (1.5%)
Bare metal stent	88/1,014 (8.7%)	134/1,243 (10.8%)	64/756 (8.5%)	64/756 (8.5%)
Drug eluting stent	902/1,014 (89.0%)	1,073/1,243 (86.3%)	678/756 (90.0%)	678/756 (90.0%)
Both bare metal and drug eluting stent used	<11	<11	<11	<11
			0.802	> 0.99

* A history of dyslipidemia is defined per the NCDR CathPCI registry as documentation of the following: Total cholesterol > 200 mg/dL, or low-density lipoprotein >=130 mg/dL, or high-density lipoprotein <40 mg/dL. For patients with known coronary artery disease, treatment is frequently initiated for low-density lipoprotein >100 mg/dL, thus qualifying for hypercholesterolemia.¹²