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Comparative Effectiveness and Safety of Prasugrel versus Ticagrelor following Percutaneous Coronary Intervention: An Observational Study

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PHARMACOTHERAPY

Comparative Effectiveness and Safety of Prasugrel versus Ticagrelor following Percutaneous Coronary Intervention: An Observational Study

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Abstract:	Background: Observational studies comparing ticagrelor and prasugrel in this setting have yielded contradictory results but often do not consider differential censoring (e.g., for treatment switching or insurance disenrollment)or confounding by time dependent factors. Objective: Our objective was to conduct a comparative effectiveness and safety analysis of ticagrelor and prasugrel in patients who underwent PCI after being hospitalized for an acute coronary syndrome. Methods: This study used the Optum's de-identified Clinformatics® Data Mart Database and included patients aged 18 years or older with an index hospital admission between May 2012 and December 2015, a diagnosis of acute coronary syndrome managed with percutaneous coronary intervention, and treatment with either ticagrelor or prasugrel. The primary composite outcome was defined as the first occurrence all-cause death, myocardial infarction, or ischemic stroke. The secondary composite outcome included the first occurrence of gastrointestinal bleed, intracranial hemorrhage, or other major bleeds requiring hospitalization. Weighted Cox proportional hazard models and robust variance estimation were implemented to adjust for baseline comorbidities, time-varying exposure, time-dependent confounders, and differential censoring. Results: Included in the analysis were 2,559 patients initiated on

	ticagrelor and 4,456 patients initiated on prasugrel following PCI. Patients initiated on ticagrelor were 10% more likely to have eligibility disenrollment (Ticagrelor: 57%, Prasugrel: 47%, P<.01) and 7 percentage-points more likely to switch medication (Ticagrelor: 35%, Prasugrel: 28%, P<.01). After adjusting for multiple factors, including time-varying exposure, and censoring imbalance, ticagrelor use was associated with a higher risk of all-cause death, MI, or stroke when compared to prasugrel (HR: 1.33; 95%CI: 1.04-1.68). Similarly, ticagrelor was associated with a higher risk in bleeding events when compared with prasugrel (HR: 1.61; 95%CI: 1.19-2.17). Conclusion: When compared with ticagrelor, prasugrel use following PCI for ACS was associated with a lower risk of death, MI, or stroke. as well as with a reduced risk of major bleeding.

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Title: **Comparative Effectiveness and Safety of Prasugrel versus Ticagrelor following Percutaneous Coronary Intervention: An Observational Study**

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ABSTRACT

Background: Observational studies comparing ticagrelor and prasugrel in this setting have yielded contradictory results but often do not consider differential censoring (e.g., for treatment switching or insurance disenrollment)or confounding by time dependent factors.

Objective: Our objective was to conduct a comparative effectiveness and safety analysis of ticagrelor and prasugrel in patients who underwent PCI after being hospitalized for an acute coronary syndrome.

Methods: This study used the Optum's de-identified Clinformatics® Data Mart Database and included patients aged 18 years or older with an index hospital admission between May 2012 and December 2015, a diagnosis of acute coronary syndrome managed with percutaneous coronary intervention, and treatment with either ticagrelor or prasugrel. The primary composite outcome was defined as the first occurrence all-cause death, myocardial infarction, or ischemic stroke. The secondary composite outcome included the first occurrence of gastrointestinal bleed, intracranial hemorrhage, or other major bleeds requiring hospitalization. Weighted Cox proportional hazard models and robust variance estimation were implemented to adjust for baseline comorbidities, time-varying exposure, time-dependent confounders, and differential censoring.

Results: Included in the analysis were 2,559 patients initiated on ticagrelor and 4,456 patients initiated on prasugrel following PCI. Patients initiated on ticagrelor were 10% more likely to have eligibility disenrollment (Ticagrelor: 57%, Prasugrel: 47%, P<.01) and 7 percentage-points more likely to switch medication (Ticagrelor: 35%, Prasugrel:

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Conclusion: When compared with ticagrelor, prasugrel use following PCI for ACS was associated with a lower risk of death, MI, or stroke. as well as with a reduced risk of major bleeding.

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INTRODUCTION

Dual antiplatelet therapy (DAPT), with aspirin and a $P2Y_{12}$ agent, reduces the risk of subsequent ischemic events and is a mainstay in treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI).[1–3] In the TRITON-TIMI-38 trial, less ischemia but more bleeding occurred in the prasugrel than clopidogrel group. In contrast, in the PLATO trial comparing ticagrelor and clopidogrel, both agents reduce CV death, MI, and stroke by the same magnitude and both agent increase non-CABG TIMI major bleeding by the same magnitude.. The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial, a randomized, open-label study evaluating ticagrelor versus prasugrel in patients with acute coronary syndrome (ACS) in whom an invasive evaluation was planned, found that patients receiving ticagrelor had a significantly higher incidence of death, myocardial infarction, or stroke but similar rates of major bleeding over 1 year of follow up.[4] Observational studies comparing ticagrelor and prasugrel in this setting have yielded contradictory results, [5–9] but have not taken into account the possibility of differential censoring (e.g., for treatment switching or insurance disenrollment), nor of confounding by time dependent factors, both of which can affect study outcomes.[10]

We conducted a comparative effectiveness and safety analysis of ticagrelor and prasugrel in patients who underwent PCI for an acute coronary syndrome. We implemented marginal structural models and employed inverse probability censoring weighting to adjust for post-treatment selection bias caused by imbalance in treatment

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switching and insurance disenrollment between comparison groups. We hypothesized that after adequate adjustment for confounding and selection bias, a real-world comparative effectiveness and safety study would yield results similar to those observed in the ISAR-REACT 5 trial.

METHODS

Data Source

We utilized Optum's de-identified Clinformatics® Data Mart Database (Optum Inc., Eden Prairie, MN), a large, nationwide, managed care, administrative claims dataset comprised of longitudinal medical billing information in the United States. Insurance claims for all pharmacy, inpatient, and outpatient services are included for the enrolled 13 million yearly-members.[11] This project was designated as "research not involving human subjects" by the University of Rhode Island Institutional Review Board, as all data were de-identified prior to analyses.

Study Cohort

Patients aged 18 years and older hospitalized between May 2012 and September 2015 with a diagnosis of ACS managed with PCI and treated with either prasugrel or ticagrelor were included. This period was selected to align with the FDA approval of ticagrelor in July 2011, allowing for delayed acceptance into insurance formularies. ACS was identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (ICD-9-CM: *410.x [acute myocardial infarction] and 411.x[other acute and subacute forms of ischemic heart disease]*).[12]

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PCI was identified by ICD-9-CM and Current Procedural Terminology (CPT-4) procedure codes (*ICD-9-CM: 00.66, 36.01, 36.02, 36.05, 36.06, 36.07, and 36.09; CPT-4: 92980, 92981, 92982, 92984,* 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92973) occurring during the index hospitalization.[9] At least one pharmacy prescription claim for either ticagrelor or prasugrel within 14 days of discharge was required.[9] Patients with prior dispensing of ticagrelor or prasugrel, history of stroke, fibrinolytic therapy within one day of hospitalization, prior dispensing of oral anticoagulants, or dispensing of strong Cytochrome P-450 3A inhibitors/inducers identified during the baseline period were excluded.[4,13] Additionally, patients with claims for more than one or any non-study antiplatelet agents during the 14-day initiation window were excluded.

Outcomes Assessments

The primary composite outcome was defined as the first occurrence of one of any of the following: all-cause death, myocardial infarction, or ischemic stroke. All-cause death was identified utilizing the Social Security Administration's Death Master File. Since only the month and year of death were included in these data, a day of death was randomly assigned within each month for death events occurring after hospital discharge. Myocardial infarction and stroke were identified by ICD-9-CM diagnosis codes (*MI: 410-412 [excluding 410.x2]; Stroke: 430-434, 436*) occurring during hospitalization.[14,15] The secondary composite outcome was defined as the first occurrence of one of the following: gastrointestinal bleed, intracranial hemorrhage, or other major bleeding requiring hospitalization.[16] Patients were followed from index

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hospitalization discharge until primary endpoint occurrence, loss of insurance eligibility, or for 365 days; whichever occurred first.

Censoring Assessment

Censoring events included insurance disenrollment, treatment switching, treatment discontinuation, or end of data window on September 30, 2015. Insurance disenrollment was identified by eligibility end or a gap of 30 days or more in insurance enrollment. Treatment switching was classified by the discontinuation of the initially prescribed antiplatelet therapy and initiation of an alternative medication, as identified via prescription pharmacy claims. Patients who switched to ticagrelor or prasugrel were not censored at switch date consistent with the time-varying exposure analysis described below. However, patients that switched to clopidogrel were censored. Therapy discontinuation was defined as a greater than 45 days of gap between prescription end of supply and refill. Since treatment duration of 6 to 12 months is recommended in this clinical setting, gaps greater than 45 days occurring after 6-months of follow-up were not evaluated.[17]

Covariate Assessment

Baseline covariates assessed during the 6-month baseline window included: age, sex, hypertension, tobacco use, hyperlipidemia, major bleeding, peripheral vascular disease, chronic kidney disease, dialysis, anemia, chronic obstructive pulmonary disease, previous percutaneous transluminal angioplasty, previous coronary artery bypass graft, congestive heart failure, atrial fibrillation, and beta-blocker, diuretic, statin, proton-

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pump inhibitor, or diabetes medication use. These are time-fixed potential confounding factors specified by previous studies. [17,18] A time variable was generated for each person-time interval when the exposure was assessed. Angina, prior interval treatment, and interval time were included as time-dependent covariates assessed during each month of follow-up.

Statistical Analysis

Categorical variables are presented as frequencies (%) and compared using chi-square tests. Continuous variables are presented as mean ± standard deviation (SD) and were compared between two drug groups using student t-test. Marginal-structural models (MSM) were fit using inverse probability weights (IPW) to adjust for confounding with time-dependent variables.[19,20] Possible violations of positivity and misspecification were assessed in all models by inspecting the estimated stabilized weight distribution to check for extreme values and to confirm that the mean was approximately equal to one.[21] The proportional hazards assumption was assessed graphically by examining the IPW log cumulative hazard function estimates to ensure that the hazard curves remained parallel over time.

Time-Dependent Exposure (TD)

Weighted Cox proportional hazard models and robust variance estimation were implemented to adjust for baseline and time-dependent confounders.[22,23] The robust variance estimator was required to account for the additional variability introduced by estimating the IPWs. The time-dependent weights were constructed to adjust for fixed

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baseline and time-varying confounding factors. Exposure was assessed at monthly intervals of prescription dispensing for each patient following initial assignment and continued until loss of eligibility, switching to clopidogrel, treatment discontinuation, event occurrence, or study end. Weights for each person-time interval were created by the ratio of the probability that each patient received their observed treatment conditional on time, and past treatment divided by the probability that the patient received the observed treatment given time, past treatment, baseline covariates, and prognostic (time-dependent) factors.[24]

Censoring Weighting (CW)

The censor-weighting accounted for possible informative censoring (e.g., insurance disenrollment) due to measured confounding factors. These weights were estimated as the ratio of the probability of remaining enrolled in the insurance program for 12-months following index hospitalization given time of the exposure assessed, prior treatment divided by the conditional probability of remaining enrolled given time, prior treatment, baseline variables, and time-dependent confounding factors.[24,25] The time-dependent exposure and censoring weights were multiplied together for each person-time interval of follow-up for each patient.

Sensitivity Analyses

Intention-To-Treat Analysis (ITT)

A conventional ITT analysis was conducted to better enable comparison with the approaches used in previously published observational studies. Patients were censored

For Peer Review

if loss of follow-up due to insurance disenrollment but were not censored based on treatment discontinuation, adherence, or switching. The IPWs were derived by a ratio of the marginal probability of exposure and the probability of exposure given baseline covariates.[26] The weights were used to create a pseudopopulation in which the measured covariates and treatment assignment were independent of each other. No adjustments were made for time-dependent confounding factors. We hypothesized that not adjusting for dropout or switching imbalances between exposure groups would bias results toward the null.

Clopidogrel Naïve Population

To determine if clopidogrel exposure during baseline period was associated with the study outcomes, we narrowed the population to antiplatelet-naïve patients by excluding those with clopidogrel exposure during the baseline period. While the ISAR-REACT 5 trial did not exclude patients with a history of clopidogrel use, we hypothesized that the results would be similar for a population that was naïve to $P2Y_{12}$-antiplatelet therapy.

RESULTS

Study Population

There were 91,682 individuals admitted with an ACS who underwent PCI during the study period. Of these, 71,287 had 6-months of insurance eligibility prior to index hospitalization. After applying the exclusion criteria, there were 2,559 initiated on

For Peer Review

ticagrelor and 4,456 initiated on prasugrel following PCI who were included in this analysis (**Figure 1**).

The ticagrelor group had significantly higher incidences of comorbidities at baseline as compared with those who initiated prasugrel (**Table 1**). The ticagrelor group was older, had higher rates of hypertension, chronic kidney disease, anemia, chronic obstructive pulmonary disease, congestive heart failure, and atrial fibrillation. Patients initiated on ticagrelor were 10% higher on eligibility disenrollment and 7% higher on medication switching (absolute differences in **Table 2**). The ticagrelor group had a 2 percentage-point higher use of clopidogrel during baseline compared to the prasugrel group (absolute differences in **Table 2**). Treatment discontinuation was balanced between groups.

Comparative Effectiveness Results

In the unadjusted analysis, the composite outcome, death, myocardial infarction, or ischemic stroke, occurred numerically more often in the ticagrelor group (**Table 3**). The rates of gastrointestinal bleeding, intracranial hemorrhage, and other major bleeding requiring hospitalization were also numerically greater in the ticagrelor group, however neither difference in composite endpoint rates was statistically significant. After adjusting for multiple confounding factors, time-varying exposure, and censoring imbalance, ticagrelor was associated with a higher risk of the composite all-cause death, MI, or stroke, when compared to prasugrel (HR: 1.33; 95%CI: 1.04-1.68; p=0.02) (**Table 4**). Similarly, ticagrelor was also associated with a higher risk of bleeding events

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(HR: 1.61; 95%CI: 1.19-2.17; p<0.01). Figures 2 and 3 show the survival curves for outcomes in the IPW estimated pseudopopulation.

Sensitivity Analysis Results

Intention-To-Treat Analysis (ITT)

The conventional ITT analysis that did not adjust for the disenrollment or switching imbalance between groups derived estimates in the opposite direction. With the ITT approach, ticagrelor was associated with numerically fewer all-cause death, MI, and stroke events (HR: 0.78; 95%CI: 0.58-1.06; p=0.11) and numerically fewer bleeding events (HR: 0.84; 95%CI: 0.58-1.20, p=0.33), but these differences were non-significant.

Clopidogrel Naïve Population

Results for the sensitivity analyses that excluded patients dispensed clopidogrel during baseline were similar to those from the ISAR-REACT 5 study population, where prior clopidogrel use was allowed. The TD-CW method for ischemic (HR: 1.28; 95%CI: 0.99-1.66; p=0.06) and bleeding (HR: 1.63; 95%CI: 1.19-2.23, p<0.01) composite outcomes remained consistent. Similarly, ITT results for the primary composite outcome (HR: 0.81; 95%CI: 0.59-1.11; p=0.19) and secondary composite outcome (HR: 1.05; 95%CI: 0.73-1.51; p=0.79) were similar in direction although not significantly different.

DISCUSSION

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In this real-world study using a national claims dataset we compared the incidence of composite ischemic and bleeding events between hospitalized patients prescribed ticagrelor or prasugrel after PCI for an ACS. Two analytic methods were applied. In TD-CW analyses with Marginal Structural Models, ticagrelor was associated with a 33% increased hazard of all-cause death, MI, or stroke, as well as a 61% greater hazard for ICH, GI bleed, or major hemorrhage. However, in traditional ITT analyses there were no significant differences in ischemic or bleeding outcomes between treatments.

Our findings from the TD-CW analysis were consistent with the ISAR-REACT 5 trial which found that prasugrel was associated with a lower risk of ischemic and bleeding events in patients treated for ACS. While treatment guidelines recommend prasugrel or ticagrelor equally following PCI, many clinical and non-clinical factors can influence treatment selection, potentially explaining the observed imbalances in disenrollment and antiplatelet switching.[17,27] While observational studies can adjust for baseline imbalances between groups, post-exposure events are not often evaluated. We implemented a time-dependent exposure and censor weighted model to adjust for the censoring imbalances identified in Table 2. In order to replicate/mimic findings from the RCT, we need to conduct a study in which adherence is similar. To do this, we need to account for time-varying confounding and censoring to get an accurate 'on treatment' effect. Thus, we applied methods for time-dependent confounding, drug switching and discontinuation to account for differences in adherence/discontinuation between the

For Peer Review

real-world data and RCT. Accounting for these factors within the observational cohort resulted in dropout and treatment switching rates that were similar to the ISAR-REACT 5 trial. The results from this analysis were in the same direction as the trial results.

The observational literature regarding outcomes of antiplatelet use have conflicting results.[5–9,18,28] Differences in how study designs address variability in follow-up time, inclusion and exclusion criteria, approaches for addressing covariates may lead to divergent conclusions. Using a conventional ITT analytic approach that fails to address censoring events that are imbalanced between treatment groups, and differential censoring can lead to different interpretations of the estimates. Dawwas et al. evaluated the comparative effectiveness and safety of ticagrelor versus prasugrel in patients with ACS.[28] Their results indicated that ticagrelor was associated with a decreased risk of recurrent nonfatal CVD events (HR: 0.80, 95%CI: 0.70-0.92), and major bleeding events (HR: 0.54, 95%CI: 0.41-0.70). In contrast, some observational studies suggested a benefit with prasugrel over ticagrelor. For example, Larmore et al. found that major adverse cardiovascular and major bleeding events were lower at 30-days in the prasugrel-treated group when compared to the ticagrelor-treated group.[29] However, most observational studies found no significant difference in the incidence of adverse cardiovascular and bleeding events when comparing these agents.[7-11] Our ITT sensitivity analysis provided results that were consistent with recent observational studies evaluating these agents and that were contrary to the ISAR-REACT 5 trial. Ignoring differential post-assignment imbalances between exposure groups produced results in the opposite direction. The variability of results in observational studies may

For Peer Review

be attributed to different study populations, and most likely unaddressed post-treatment selection bias as none of these studies assessed or compared medication switching or disenrollment rates in comparison groups during study follow-up.

While there was a statistically significant 2% higher clopidogrel exposure rate in the ticagrelor group during the baseline period , narrowing the population to antiplatelet-naïve patients by excluding those with prior clopidogrel exposure produced similar results with a slight loss in power. This suggests that clopidogrel use at baseline period did not impact the estimated treatment effect.

The key difference between the analysis methods lies in adjusting for confounding that results in incomplete adherence to the assigned treatment. It has been noted in clinical trials that loss to follow-up may be affected by clinical or demographical factors occurring after randomization. Our results further confirmed that the imbalance of medication switching or insurance disenrollment between exposures could bias the results. Adjusting for post-assignment factors can help improve the precision of effect estimates. After adjusting for time-varying confounding and treatment in the TD-CW analysis, our findings were consistent with the ISAR-REACT 5 trial where the post-treatment selection bias was addressed.

LIMITATIONS

First, this study is based on claims data and could be biased by unmeasured confounding factors (e.g., over-the-counter medications, antiplatelet loading-dose, or other details of

For Peer Review

inpatient procedures). Second, a substantial number of patients were excluded for not having an outpatient dispensing of the study treatment within 14-days of index PCI. Subsequent analysis of the 27,049 patients excluded indicated that the majority did not have pharmacy dispensings of the study agents. The 14-day window captured >83% of the patients with pharmacy dispensing of the study treatments in the database. We presume that most of the patients with no dispensings of antiplatelet agents following PCI were treated and recorded using a different payment system. Increasing this window to 30 and 90 days did not greatly improve the number of patients identified. However, these effects are thought to be non-differential as we are comparing two drugs from the same drug class. Third sub-codes differentiating between types of myocardial events such as STEMI or NSTEMI were not reliably utilized in the data to differentiate as outcomes. Fourth, our results pertain to patients enrolled in a managed care plan and may not be generalizable to other populations. Additionally, the death file included within this dataset is the Social Security Administration Death Master file. Since 2013 it was no longer mandatory for states to report death events to the Social Security Administration. As such, death events are expected to be non-differentially underreported.[30] Lastly, there are several key assumptions that must be made to obtain correct causal inferences from the time-varying approaches. We assumed that the measured covariates, including baseline and time-varying factors, were sufficient to adjust for both confounding and post-treatment selection bias. This assumption is not testable in retrospective observational studies; however, we relied on comprehensive literature review and clinical expertise to bolster this assumption. While many of the covariates were selected to mimic previous clinical trials, information regarding

For Peer Review

gastrointestinal disorders or abnormalities may be factors of interest for future studies. We also assumed that the models implemented were suitably specified, including the MSM comparing average treatment effects conditional on time-varying exposure, baseline covariates, and time-varying confounders. While these assumptions are not testable, we fit the same covariates in all models to make these results comparable.

CONCLUSION

After adjusting for confounding factors, time-varying exposure, and censoring imbalance using marginal structural models with TD-CW, results from our observational data mirrored those from a contemporary randomized controlled trial asking the same question; application of such statistical methods may augment future comparative effectiveness and safety analyses using observational data.

For Peer Review

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For Peer Review

Figure 1. Study Population

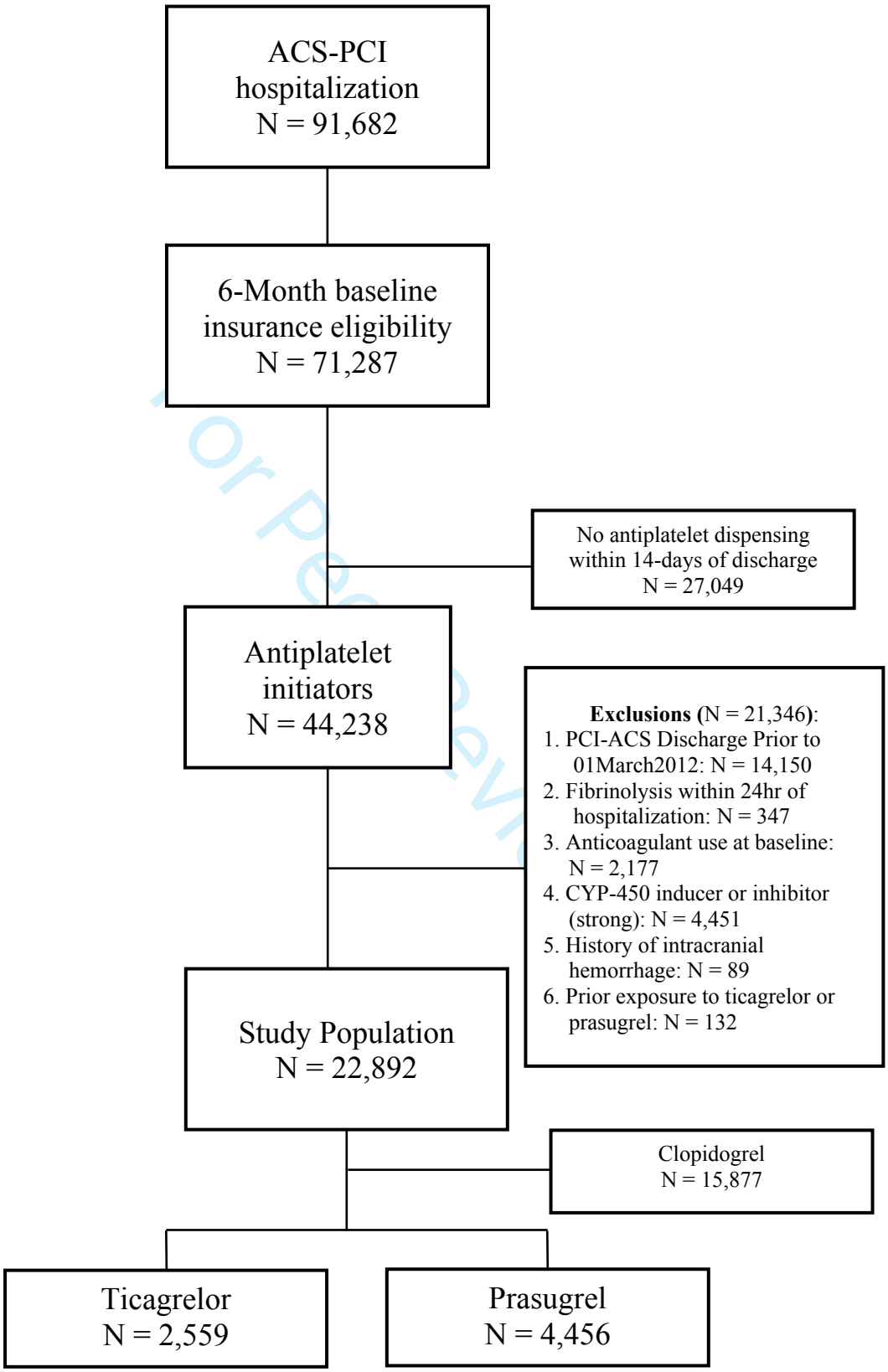


Table 1. Baseline Characteristics by Initial Exposure

Characteristics	Ticagrelor (%) n = 2,559		Prasugrel (%) n = 4,456		P
Age (±SD)	65.3	±11.7	59.8	±10.2	<0.01
Female	820	(31)	968	(21)	<0.01
Tobacco Use	633	(24)	1,195	(26)	0.04
Hypertension	2,041	(77)	3,233	(71)	<0.01
Hyperlipidemia	1,916	(73)	3,338	(73)	0.64
Carotid Artery Stenosis	126	(5)	143	(3)	<0.01
Chronic Kidney Disease	231	(9)	282	(6)	<0.01
Anemia	277	(10)	308	(7)	<0.01
Chronic Obstructive Pulmonary Disease	386	(15)	503	(11)	<0.01
Asthma	133	(5)	204	(4)	0.27
Percutaneous Transluminal Coronary Angioplasty	271	(10)	410	(9)	0.07
Coronary Artery Bypass Graft	136	(5)	199	(4)	0.12
Congestive Heart Failure	514	(19)	727	(16)	<0.01
Atrial Fibrillation	199	(8)	232	(5)	<0.01
Angiotensin-Converting Enzyme/Angiotensin Receptor-Blocker	1,027	(39)	1,605	(35)	<0.01
Beta-Blocker	778	(29)	1,105	(24)	<0.01
Diuretic	425	(16)	561	(12)	<0.01
Statin	999	(38)	1,581	(35)	<0.01
Diabetic Medication	654	(25)	1,058	(23)	0.12
Proton-Pump Inhibitor	464	(18)	646	(14)	<0.01
Baseline Clopidogrel Exposure	210	(8)	278	(6)	<0.01

For Peer Review

Table 2. Censoring Frequencies by Initial Exposure

Censoring Criterion	Ticagrelor (%) n = 2,639		Prasugrel (%) n = 4,566		P Value
Days of follow-up					
Mean (±SD)	278	(± 113)	294	(± 109)	
Median (IQR)	365	(190-365)	365	(231-365)	
Insurance Disenrollment During Follow-up	1493	(57)	2139	(47)	<0.01
Medication Switch	931	(35)	1278	(28)	<0.01
Switch to Clopidogrel	815	(88)	1273	(100)	
Treatment Discontinuation	230	(9)	439	(10)	0.22

For Peer Review

Table 3. Primary and Secondary Composite Outcome Frequencies by Initial Exposure. (Unadjusted)

Outcomes	**Ticagrelor (%)** n =2,639		**Prasugrel (%)** n = 4,566		**P value**
Primary Outcomes					
All-cause Death	33	(1.3)	60	(1.3)	0.82
Myocardial Infarction	109	(4.1)	150	(3.3)	0.06
Stroke	29	(1.1)	24	(0.5)	<0.01
Death, MI, Stroke	119	(4.5)	172	(3.8)	0.12
Rate per 100 person-years	7.1 per 100 person-years		5.3 per 100 person-years		
Secondary Outcomes					
Gastrointestinal Bleed	63	(2.4)	84	(1.8)	0.11
Other Major Bleed	29	(1.1)	41	(0.9)	0.40
Intracranial Hemorrhage	11	(0.4)	17	(0.4)	0.77
Bleeding Outcomes	72	(2.7)	98	(2.1)	0.12
Rate per 100 person-years	4.7 per 100 person-years		3.3 per 100 person-years		

For Peer Review

Table 4. Adjusted Hazard Ratios for Ischemic and Bleeding Events by Analysis Methods

Time-Dependent Censor-Weighted (TD-CW)	**HR**	**95% CI**	**P**
All-cause death, MI, Stroke	1.33	(1.04 - 1.69)	0.02
ICH, GI Bleed, Major Hemorrhage	1.61	(1.19 - 2.17)	<0.01
Intention-to-Treat (ITT)			
All-cause death, MI, Stroke	0.78	(0.58 - 1.06)	0.11
ICH, GI Bleed, Major Hemorrhage	0.84	(0.58 - 1.20)	0.33
Clopidogrel-Naive TD-CW			
All-cause death, MI, Stroke	1.28	(0.99 - 1.66)	0.06
ICH, GI Bleed, Major Hemorrhage	1.63	(1.19 - 2.23)	<0.01
Clopidogrel-Naive ITT			
All-cause death, MI, Stroke	0.81	(0.59 - 1.11)	0.19
ICH, GI Bleed, Major Hemorrhage	1.05	(0.73 - 1.51)	0.79

Note: Myocardial infarction (MI), intracranial hemorrhage (ICH), gastrointestinal bleed (GI bleed)

For Peer Review

Figure 2. Estimated Survival Curve for death, myocardial infarction (MI), or stroke in weighted pseudopopulation

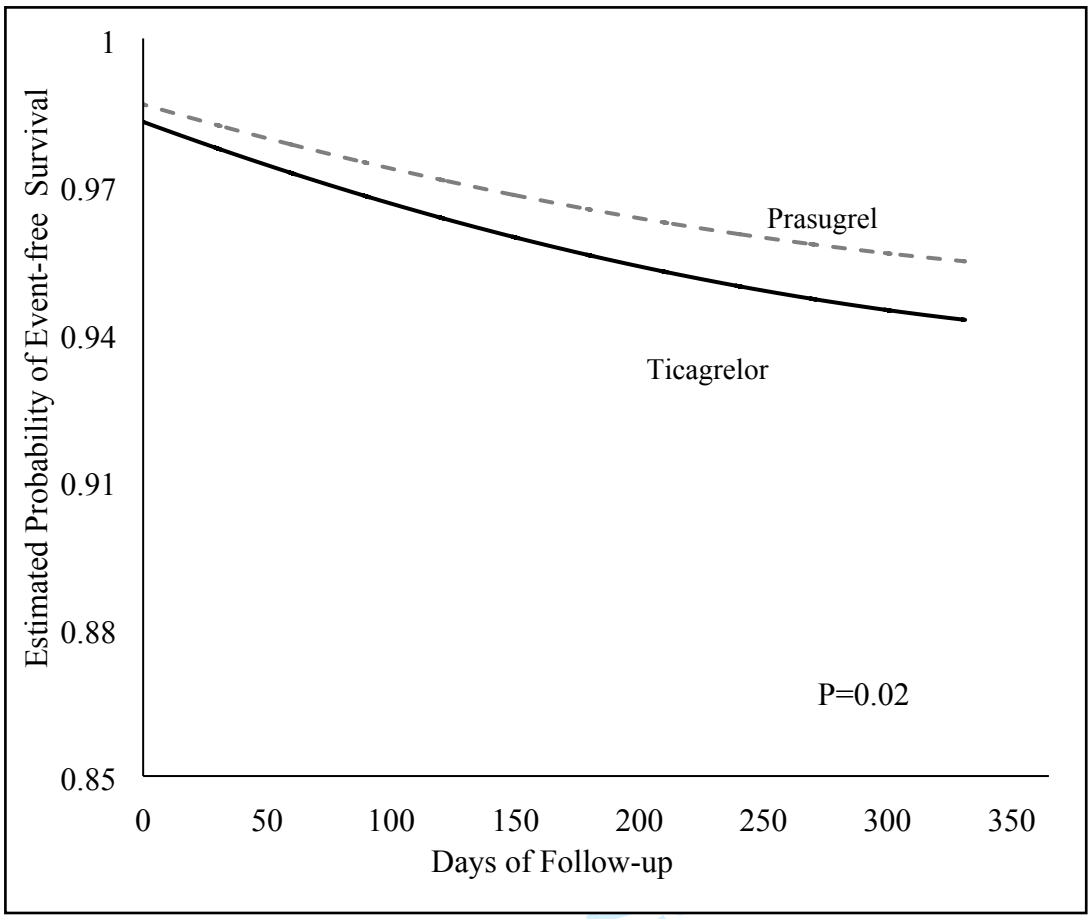
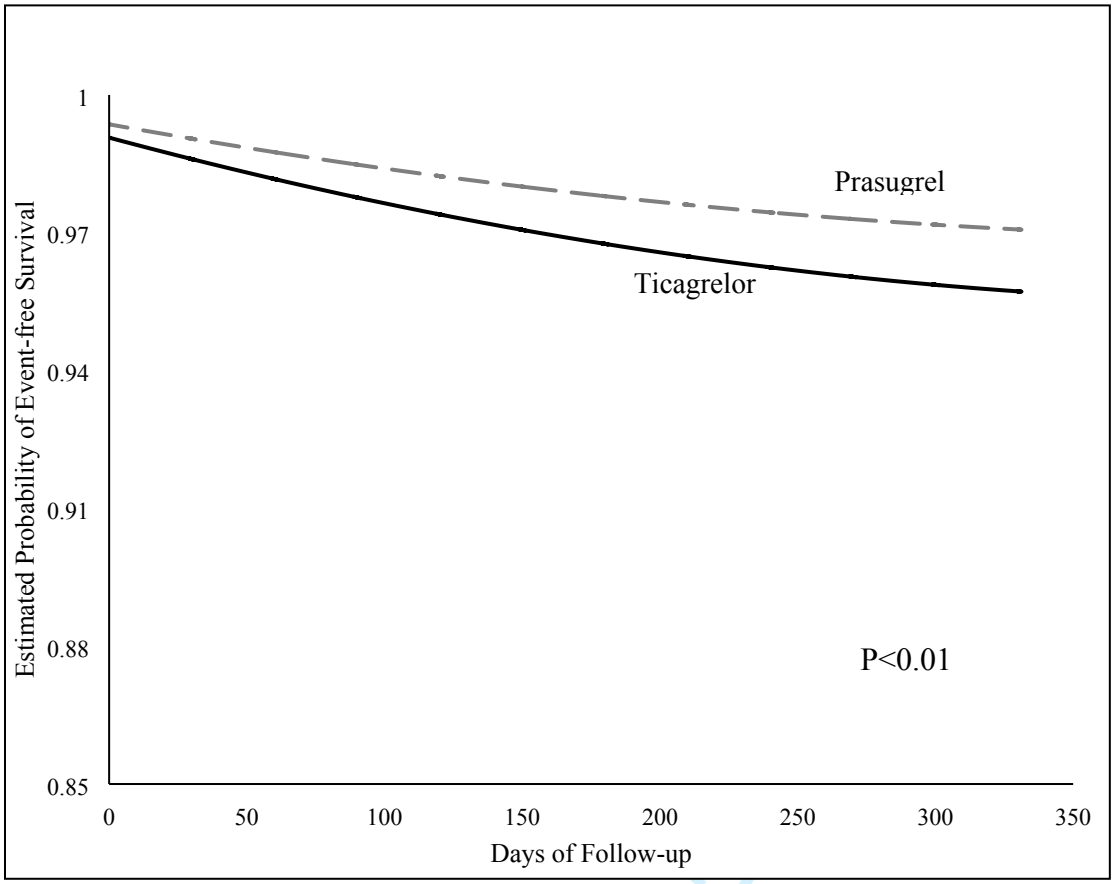


Figure 3. Estimated survival curve for gastrointestinal (GI) bleed, intracranial hemorrhage (ICH), or other major bleed requiring hospitalization in weighted pseudopopulation



Appendix:

Appendix Table 1. Baseline Covariates IDC-9 Codes:

Characteristic	ICD-9 Codes for Baseline Characteristics (decimal points removed)
Percutaneous Coronary Intervention	3601 3602 3605 3606 3607 3609 0066 92980 92981 92982 92984 92920 92921 92924 92925 92928 92933 92934 92937 92938 92941 92943 92944 92973
Acute Coronary Syndrome	410 411
Fibrinolysis	37201 37211 37212 37213 37214 37195 92977 9910
Tobacco	3051 V1582
Hypertension	4011 4019 4010 40200 40201 40210 40211 40290 40291 4030 40300 40301 4031 40310 40311 4039 40390 40391 4040 40400 40401 40402 40403 4041 40410 40411 40412 40413 4049 40490 40491 40492 40493 40501 40509 40511 40519 40591 40599 4372
Hyperlipidemia	2720 2721 2722 2723 2724
Diabetes	24900 25000 25001 7902 79021 79022 79029 7915 7916 V4585 V5391 V6546 24901 24910 24911 24920 24921 24930 24931 24940 24941 24950 24951 24960 24961 24970 24971 24980 24981 24990 24991 25002 25003 25010 25011 25012 25013 25020 25021 25022 25023 25030 25031 25032 25033 25040 25041 25042 25043 25050 25051 25052 25053 25060 25061 25062 25063 25070 25071 25072 25073 25080 25081 25082 25083 25090 25091 25092 25093
Carotid Artery Stenosis	43310 43311
Peripheral Vascular Disease	4400 4401 4402 44020 44021 44022 44023 44029 4404 4408 4409 4439 5570 5571 5579
End Stage Renal Disease	5856
Chronic Kidney Disease	585 5851 5852 5853 5854 5855 5859

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Anemia	**2800 2801 2808 2809 2810 2811 2812 2813 2814 2818 2819 2820 2821 2822 2823 2824 28240 28243 28244 28245 28246 28247 28249 2827 2828 2829 2830 2831 28310 28311 28319 2832 2839 2840 28401 28409 2841 28411 28412 28419 2842 2848 28481 28489 2849 2850 28521 28522 28529 2858 2859**
Chronic Obstructive Pulmonary Disease	**490 4910 4911 4912 49120 49121 49122 4918 4919 4920 4928 494 4940 4941 496**
Asthma	**49300 49301 49302 49310 49311 49312 49320 49321 49322 49381 49382 49390 49391 49392**
Percutaneous Transluminal Coronary Angioplasty	**V4582**
Coronary Artery Bypass Graft	**V4581**
Congestive Heart Failure	**428 4280 4281 4282 42820 42821 42822 42823 4283 42830 42831 42832 42833 4284 42840 42841 42842 42843 4289**
Atrial Fibrillation	**42731**
Intracranial hemorrhage	**431 430**

For Peer Review

Appendix Table 2. Strong CYP-450 Inhibitors and Inducers

Strong Inhibitors	Strong Inducers
CYP1A2	
FluvoxaMINE	
CYP2C8	
Gemfibrozil	
CYP2C19	
Fluconazole	Apalutamide
	RifAMPin
CYP2D6	
BuPROPion	
Dacomitinib	
FLUoxetine	
PARoxetine	
QuiNIDine	
Tipranavir	
CYP2E1	
Disulfiram	
CYP3A4	
Atazanavir	Apalutamide
Clarithromycin	CarBAMazepine
Cobicistat	Enzalutamide
Darunavir	Fosphenytoin
Idelalisib	Lumacaftor
Indinavir	Mitotane
Itraconazole	PHENobarbital
Ketoconazole (Systemic)	Phenytoin
Lopinavir	Primidone
MiFEPRIStone	RifAMPin
Nefazodone	
Nelfinavir	
Ombitasvir, Paritaprevir, and Ritonavir	

For Peer Review

Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir
Posaconazole
Ritonavir
Saquinavir
Telithromycin
Voriconazole

For Peer Review

05-Jan-2021

Dear Dr Wen:

Manuscript ID 12-20-0746 entitled "Comparative Effectiveness and Safety of Prasugrel versus Ticagrelor following Percutaneous Coronary Intervention: A Real-World Data Study" which you submitted to Pharmacotherapy, has been reviewed. The comments of the reviewers are attached to this letter.

The reviewers have concerns with your paper, and major revisions would be needed to make it acceptable. Therefore, if you choose to make such changes to your paper and resubmit it, you must respond to the reviewers' comments and revise your manuscript accordingly. Your paper may be acceptable for publication provided you can satisfactorily respond to the reviewers' comments.

Please be mindful of word and reference counts when preparing your revision. You should refer to the author instructions for more information regarding word and citation limits.

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When submitting your revised manuscript, please upload a Word file that includes a copy of the reviewers' comments and your responses to these comments (highlighted). Please name this file "Response to Comments" and upload it as a "Supplementary" file. You can use this file to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewers' comments.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer.

To submit your revised manuscript, log into https://urldefense.proofpoint.com/v2/url?u=http-3A__mc.manuscriptcentral.com_pharmacotherapy&d=DwIFaQ&c=dWz0sRZOjEnYSN4E4J0dug&r=132BPCjAOTejTEebG8o5vFDgJj9BGfyfjtxESqsz3yc&m=_knkB6GLMGH6Im-

nMxWLsELuOsr_U9fK5XtkzoAnTkk&s=E7qP-3FGROSQNfOW-y7WlsVyduR3Uto30WM5D4g3cAU&e= and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

I would very much appreciate it if you could upload your revision by **06-Mar-2021**. If it is not possible for you to submit your revision in a reasonable amount of time (i.e., within 4 months) we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to Pharmacotherapy and I look forward to receiving your revision.

Cordially,

James Tisdale, PharmD
Scientific Editor, Pharmacotherapy
jtisdale@purdue.edu

Response: We sincerely appreciate the reviewer' constructive comments and editor's consideration. We will address all comments and resubmit the revised manuscript and point-to-point responses.

Reviewer(s)' Comments to Author:
Reviewer: 1

Comments to the Author
This manuscript is a real-world comparative effectiveness study of prasugrel and ticagrelor for ACS with PCI.
1. Abstract: Please include a brief Background section.

Response: Added a background section to abstract

2. Page 8: Methods, Covariate Assessment - why wasn't STEMI, NSTEMI or unstable angina NOT included in the analysis? It is a predictor of outcome. If you were not able to discern from the database, describe in the limitations.

Response: Sub-codes differentiating between types of myocardial events such as STEMI or NSTEMI are not reliably utilized to differentiate as outcomes.[1]

3. Limitations Page 16: Exclusion Criteria/Figure 1: I calculated that 38% of patients in the database were excluded for lack of 14-day dispensing which is capturing 72% not 83%. Please reconcile.

For Peer Review

Response: **Updated the language in the limitations section to make clearer. The 14-day window identified 83% of the patients within the database that had a pharmacy dispensing for the study treatment following PCI. During post-hoc analysis of the 27,049 patients excluded, only 10% had prescription dispensing for study agents at anytime following PCI, with 3-5% having dispensings within 15 to 90-days. Thus, using the 14-day window, we identified most of the patients with evidence of initiation of study treatment following PCI. Most of the 27,049 excluded did not have claims for the therapies of interest.**

4. Figure 1: Where are those patients with PRIOR dispensing (page 7 line 15) in your figure?

Response: **There were 70, 27, and 35 patients in prasugrel, ticagrelor, and clopidogrel groups that had prior dispensings to either prasugrel or ticagrelor respectively. These patients were grouped with prior antiplatelet exclusion. Figure 1 has been updated to reflect this.**

5. Exclusion Criteria/Figure 1: What were the strong CYP3A inducers and inhibitors prescribed? Figure 1 indicates 5-10% of patients were excluded. In practice those amount to clarithromycin and rifampin. Neither of which in my experience are prescribed often. Please re-evaluate these medications. Or did you mean moderate and strong?

Response: **Patients taking strong CYP inducers or inhibitors were excluded (any CYP Isoenzyme, not just 3A4). A list is provided at the end of this document. The language was fixed in the manuscript.**

6. Table 1: Please include whether the patient had STEMI, NSTEMI or unstable angina.

Response: **STEMI and NSTEMI cannot be precisely assessed in the claims data. Sentence added in the limitations section.. No evidence has shown that STEMI, NSTEMI, or unstable angina significantly related to prescribing of two study drugs.**

7. Table 3: You need to either define Composite Outcomes or change the labels. Consider redefining primary outcome as primary efficacy outcomes and secondary as secondary bleeding outcomes. As is, you have two labels: Composite Outcome that have different meanings.

Response: **Edited table 3 so that outcomes are clearer.**

8. All patients were followed for various times, correct? What was the median for each group? Add to the results. More importantly, why aren't the results presented in annualized events or per patient per some time period? (Tables 2 and 3) If it is taken into consideration in the analysis, please explain it more clearly in the methods.

Response: **FU time is Added to table 2. Results as rate per person-time added to table 3.**

For Peer Review

9. Figures 2 and 3 are not mentioned in the manuscript. Should they be? If not, delete.
Response: **Sentence added at the end of the results section.**

Reviewer: 2

Comments to the Author
General comments to the authors:

I would like to congratulate the authors on an interesting and timely manuscript. Overall, the paper is well written with some specific revisions discussed below. Here are some general comments on the manuscript:

1. The major issue with the manuscript is a thorough explanation of how and why their specific time exposure and censoring weighting methods impact the data findings. The data presented shows that it changes the interpretation of the data, but the reader does not gain an understanding of why and how the data changed. I would highly recommend more explanation of these methods, possible providing an example of how and why these methods change the findings in the introduction or discussion.

Response: **Thank you for your important suggestion. We have added a sentence at the end of the second paragraph of the discussion section: "In order to replicate/mimic findings from the RCT, we need to conduct a study in which adherence is similar. To do this, we need to account for time-varying confounding and censoring to get an accurate 'on treatment' effect. Thus, we applied methods to account for time-dependent confounding, drug switching and discontinuation to account for differences in adherence/discontinuation between the real-world data and RCT. Accounting for these factors within the observational cohort resulted in dropout and treatment switching rates that were similar to the ISAR-REACT 5 trial. The final results from this analysis were in the same direction as the trial results We also have explained in detail the time-dependent exposure and censoring weighting in the methods section.**

2. Suggest changing the title to use "an observational study" instead of "a real-world data study". Although the use of real-world seems to be popular lately, especially by pharmaceutical manufacturers, these are plain and simply observational studies.

Response: **changed to "Real-world data study".**

3. Throughout the manuscript the "12" in P2Y12 should be subscript. Also, the correct term is acute coronary syndrome and not acute coronary syndromes. It is a single syndrome. It appears in both forms throughout the manuscript.

Response: **Fixed both typos.**

Specific comments for the authors:

Page 5, lines 15-19: The statement about there not being a difference in bleeding in the PLATO trial is misleading. In practically all trials of P2Y12 inhibitors, the consistent definition of major bleeding is non-CABG TIMI major bleeding. This is what was used in TRITON-TIMI 38 and CURE. In PLATO the definition was manipulated to include all TIMI major bleeds. Since approximately 75% of patients going to CABG surgery have a major bleed, this dilutes the difference between the arms. When the consistent definition of non-CABG TIMI major bleeding is evaluated in PLATO, there is a significant increase compared to clopidogrel, with the same absolute increase as seen in TRITON. Both agents increase this consistent definition of major bleeding. Therefore, it would be appropriate to state that both agents reduce CV death, MI, and stroke by the same magnitude and both agent increase non-CABG TIMI major bleeding by the same magnitude.

Response: **Changed the statement to "both agents reduce CV death, MI, and stroke by the same magnitude and both agents increase non-CABG TIMI major bleeding by the same magnitude."**

Page 6, top: So there was no equipoise in the evaluation of your data? Then did you do a one-tailed statistical analysis?

Response: **In this observational study, there was no equipoise like there was in the RCT. Since as physicians perceived that Ticagrelor was superior to Prasugrel, there was confounding by indication which we attempted to account for through proper analysis. before ISAR-REACT 5 trial. [2–6]The final estimates are adjusted HR, which is similar as the one-tailed statistical analysis that shows the higher risk in one agent.**

Page 7, lines 10-13: It would seem more appropriate to include pharmacy claims within 30 or 45 days of discharge instead of 14 days. With many hospitals using meds-to-beds programs, the first month of medication is often provided to patients before they leave the hospital, and therefore, would not be captured in your data. Both ticagrelor and prausgrel also often gave the first month of medication for free, which would also have limited your ability to capture these patients. One of the main strengths of a comparative effectiveness study is the ability to capture larger numbers of patients than a randomized controlled trial. By limiting your pharmacy claims window, you reduce the power and impact of your results. You do mention this is your limitations, but seems to be an easy fix. It is someone confusing in your limitations discussion where you lose almost 25% of the study population because of this exclusion, but then state by changing the pharmacy claims date you did not gain many patients? These two statements do not seem to be consistent unless most of the patients did not have any claim until beyond 90 days.

Response: **We sincerely appreciate reviewer's important suggestion. We actually have examined 30 days and 45 days and didn't observe a substantial increase in sample size. Also, patients may have events within 30 days or 45 days. The 14-day window identified 83% of the patients within the database that had a pharmacy dispensing for the study treatment following PCI. During post-hoc analysis of the 27,049 patients excluded, only about 10% had prescription dispensing for study agents at any time following PCI, with 3-5% having dispensings within 15 to 90-days. Thus, using the 14-day window, we identified most of the patients with evidence of initiation of study treatment following PCI. Most of the 27,049 excluded did not have claims for the therapies of interest.**

Page 7, lines 38-43: The assigning of a random day in the month for each death seems odd. This reads as each death was given its own random day. It would seem more prudent to just give all deaths the same day of the month, such as the 1st, 15th, or 30th. This way is would be consistent for all deaths.

Response: **We sincerely appreciate reviewer's insightful comments. We considered the random date assignment a more suitable approach than using a same mid-month date. We also measured day of death using the first and last day of the month and this did not change the study results.**

Page 8, lines 22-24: Why were patients switched to only clopidogrel censored? Anytime a patients was switched, the data for that drug should end.

Response: **Patients that switched to ticagrelor or prasugrel were not censored. The risk-time attributed to the 'switched to' agent was included in estimating the pseudopopulation consistent with the time-varying exposure methods described in the statistical analysis section.**

Page 8, line 42: Not sure why COPD (or asthma in your table) are included. They are not risk factors for CVD or bleeding.

Response: **These baseline covariates have been included in other observational studies for these therapies.**

Results: Please add the mean and median follow up times for each agent.

Response: **Added to table 2.**

Limitations: It would seem that the third limitation on the counting of subsequent events could be fixed by matching additional codes with hospitalizations and not clinic visits. As well requiring a primary code for ACS on subsequent admissions. This is actually critical to the internal validity of your data.

Response: **From the reviewer's comments, we removed this limitation. The outcomes were identified via validated algorithms cited in the text evaluating hospitalizations and not clinic visits.**

References: In Pharmacotherapy the journal names are not italicized and do not have a period after them. DOI numbers are also not used by the journal. Please be sure to review the instructions to authors before your submission. In references 3-5, 8, 9, 17, 18, 25, 28, and 29 all of the words in the title are capitalized, which is not appropriate for referencing. This inconsistency should have been caught by the lead or senior authors prior to submission.

Response: **The references in the word document have no capitalizations. Perhaps this occurred during uploading or converting to PDF. I will check to be sure that this does not occur again.**

Table 2: Please add the actual event rates to this table in addition to the HR and 95% CI. Also, the HR and 95% CI do not need to all be in separate columns. This is awkward to read. They can all go in the same column.

Response: **Added event rates to table 3. Reformatted the columns in table 4.**

Figure 2 and 3: Is it appropriate to label the y-axis "estimated probability of survival" when you are not evaluating survival. Figure 2 is the composite ischemic endpoints and Figure 3 is major bleeding. May be better to label as "estimated probability event free survival"

Response: **Updated axis titles.**

Reviewer: 3

Comments to the Author
Statistical and Methodological Review

This study uses contemporary pharmacoepidemiologic methods to overcome limitations of prior studies that have evaluated the comparative effectiveness and safety of prasugrel and ticagrelor. It has many strengths. I believe a few things need to be further discussed or specified and have some relatively minor concerns about other aspects of the methods.

Response: **We sincerely appreciate the reviewer's positive comments. We will address all your comments diligently.**

The time-period of the data is not entirely clear, and this is important because of the use of ICD-9 codes to identify outcomes. The censoring criteria do not mention September 2015, the end of the study period, as a reason for censoring.

Response: **Added Data end window in the 'censoring' section of methods.**

Please comment on validation studies and the performance characteristics of the outcome definitions, i.e. PPV. I'm not entirely sure why 412, old MI, was included in that definition. 436 also is not a particularly valid code for stroke since guidance on stroke coding changed in the mid-2000s with instructions not to code strokes this way. The impact may be minimal since it is used less often, but using a study using recent data as a reference for its validity is important. It may also be useful to indicate the proportion of MIs and strokes identified with these more questionable codes. https://urldefense.proofpoint.com/v2/url?u=https-3A__www.ahajournals.org_doi_10.1161_CIRCOUTCOMES.113.000371&d=DwIFaQ&c=dWz0sRZOjEnYSN4E4J0dug&r=132BPCjAOTejTEebG8o5vFDgJj9BGfyfjtxESqsz3yc&m=_knkB6GLMGH6Im-nMxWLsELuOsr_U9fK5XtkzoAnTkk&s=SMJCj78NXlIVHAcN0At4StZQpRPeUew1FeaOqWWeYFg&e=

Response: **We evaluated outcomes as described in the cited validation algorithms.**

Please comment on the limitations of Social Security Death Index data for capturing mortality, and any validation studies vs. the National Death Index that may have been done in this data source. This data source has changed to no longer include state death data and sensitivity now appears to be limited.

Response: The death file included within this dataset is the Social Security Administration Death Master file. Since 2013 it was no longer mandatory for states to report death events to the Social Security Administration. As such, death events are expected to be non-differentially underreported.[7] This is added to the limitations with the citation.[6]

Why is angina being treated as a time-varying covariate? It seems to me that it's likely on the causal pathway from drug choice to MI since the purpose of these drugs is to prevent ischemic events. It seems reasonable to include in the analysis of bleeding since it may lead to other drugs that increase bleeding risk, but it's not clear to me why it would be considered a confounder with MI as an outcome.

Response: If a patient has an ACS, this will sometimes lead to a change in the agent used for DAPT (e.g. from prasugrel to ticagrelor).

A sensitivity analysis using only primary position MI codes may be beneficial for dealing with the challenges of differentiating visits related to prior MI and new acute MI.

Response: We utilized a validated claims algorithm for outcomes. This included MI-related hospitalization with length of stay >= 3days. Since we are not evaluating MI-related outpatient claims we believe that there is minimal opportunity for misclassifying historical MI event for a new MI event. We have removed this language from the limitations section.

The covariate list doesn't seem optimal for bleeding events, as it lacks peptic ulcer disease, inflammatory bowel disease, and some other GI abnormalities that pose bleeding risk. PPI use may handle peptic ulcer disease to some extent, but many people without peptic ulcer disease take PPIs. I'm not sure this necessitates redoing all the analyses, but can you comment on why these weren't included?

Response: We appreciate the reviewer's important suggestion. We acknowledge that these suggestions would improve the analysis. While many of the covariates were selected to mimic previous clinical trials, information regarding gastrointestinal disorders or abnormalities may be factors of interest.

Please include an appendix that specifies the ICD codes used to define different covariates, as this is necessary for reproducibility of the work and assessment of the appropriateness of the methods.

Response: Thank you for your important suggestion. We have added an eTable that present all ICD codes to define the covariates.

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Citations:

1. Alexandrescu, R., Bottle, A., Jarman, B. & Aylin, P. Current ICD10 codes are insufficient to clearly distinguish acute myocardial infarction type: a descriptive study. *BMC Health Serv Res* **13**, 468 (2013).
2. Song, C. *et al.* 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). *Am. J. Cardiol.* **120**, 1926–1932 (2017).
3. Coons, J. C. *et al.* Comparative Effectiveness and Safety Analysis of Dual Antiplatelet Therapies Within an Integrated Delivery System. *Ann Pharmacother* **51**, 649–655 (2017).
4. Yudi, M. B. *et al.* Clopidogrel, prasugrel or ticagrelor in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *Intern Med J* **46**, 559–565 (2016).
5. Alexopoulos, D. *et al.* Contemporary antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: 1-year outcomes from the GReek AntiPlatElet (GRAPE) Registry. *J. Thromb. Haemost.* **14**, 1146–1154 (2016).
6. Kim, K. *et al.* Comparative Effectiveness of Oral Antiplatelet Agents in Patients with Acute Coronary Syndrome. *Pharmacotherapy* **37**, 877–887 (2017).
7. Levin, M. A., Lin, H.-M., Prabhakar, G., McCormick, P. J. & Egorova, N. N. Alive or dead: Validity of the Social Security Administration Death Master File after 2011. *Health Services Research* **54**, 24–33 (2019).

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Appendix:

Strong CYP-450 inducers and inhibitors

Strong Inhibitors	Strong Inducers
CYP1A2	
FluvoxaMINE	
CYP2C8	
Gemfibrozil	
CYP2C19	
Fluconazole	Apalutamide
	RifAMPin
CYP2D6	
BuPROPion	
Dacomitinib	
FLUoxetine	
PARoxetine	
QuiNIDine	
Tipranavir	
CYP2E1	
Disulfiram	
CYP3A4	
Atazanavir	Apalutamide
Clarithromycin	CarBAMazepine
Cobicistat	Enzalutamide
Darunavir	Fosphenytoin
Idelalisib	Lumacaftor
Indinavir	Mitotane
Itraconazole	PHENobarbital
Ketoconazole (Systemic)	Phenytoin
Lopinavir	Primidone
MiFEPRIStone	RifAMPin
Nefazodone	
Nelfinavir	

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Ombitasvir, Paritaprevir, and Ritonavir	
Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir	
Posaconazole	
Ritonavir	
Saquinavir	
Telithromycin	
Voriconazole	

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