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THE COMPARATIVE EFFECTIVENESS, SAFETY, AND COST OF ORAL P2Y12 ANTIPLATELET AGENTS FOLLOWING ACUTE CORONARY SYNDROMES

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BY

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ABSTRACT

Over 1 million individuals in the United States experienced a coronary event during 2019. Following an acute coronary syndrome, patients are initiated on dual antiplatelet therapy consisting of aspirin plus a P2Y12 agent to reduce the risk of subsequent ischemic events. In this dissertation we use the three-manuscript format to address some areas of unmet research related to this therapeutic area. Each manuscript has an abstract, introduction, methods, results, discussion, limitations, and conclusion section.

Manuscript 1: We examined the performance of several different causal modeling approaches to real-world data with the objective of addressing selection bias in the presence of differential treatment nonadherence in comparative effectiveness research. We compared the treatment effect estimates of ticagrelor versus clopidogrel following an acute coronary syndrome by applying several analytical approaches, each with different levels of adjustment for confounding and treatment nonadherence, to the previously published "PLATO" randomized control trial where there was negligible differences in protocol adherence among treatment groups. We found that applying a time-dependent exposure model adequately adjusted for the imbalance in rate of therapy switching and produced an effect estimate congruent to the PLATO trial.

Manuscript 2: Our objective was to conduct a comparative effectiveness and safety analysis of ticagrelor and prasugrel in patients who underwent percutaneous coronary intervention after being hospitalized for an acute coronary syndrome. We implemented marginal structural models and inverse probability censoring weighting to adjust for post-treatment selection bias caused by imbalance in treatment switching and insurance disenrollment between comparison groups. We found that implementing a time-

dependent exposure and censor-weighted model, to adjust for the censoring imbalances observed in the real-world data cohort, derived results consistent with the recently published ISAR-REACT 5 trial. We also found that applying traditional approaches derived results that were consistent with previously published observational studies but contrary to the RCT.

Manuscript 3: Our objective was to compare the direct health system costs and healthcare resource utilization associated with escalating to either ticagrelor or prasugrel following initial clopidogrel treatment due to an acute coronary syndrome. Median per-member per-month all-cause and cardiovascular-related charges and healthcare utilization were evaluated for each patient following escalation. Propensity-score 1:1 greedy matching was used to adjust for confounders. Generalized linear models were used to derive an effect estimate of treatment escalation on outcomes. We found that patients who escalate antiplatelet therapy from clopidogrel to ticagrelor experienced lower total all-cause costs and cardiovascular-related costs when compared to those that escalated to prasugrel

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PREFACE

This dissertation is written in the manuscript format and is comprised of three manuscripts dealing with different aspects of the comparative effectiveness, safety, and costs associated with P2Y12-inhibitor antiplatelet therapy following acute coronary syndromes.

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MANUSCRIPT 1

Title: **Addressing Time-Dependent Selection Bias in Comparative Effectiveness Research: An Example Comparing Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes**

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The 35th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Philadelphia, PA, USA

ABSTRACT

Objective: Our objective was to evaluate the comparative effectiveness of clopidogrel and ticagrelor in a population similar to the PLATO randomized controlled trial while exploring methodologies that best account for imbalanced treatment switching and dependent censoring imposed observed in the real-world data.

Methods: This study used the Optum Clinformatics Datamart and included patients aged 18 years or older with an index hospital admission between May 2012 and December 2015. Patients with a diagnosis for an acute coronary syndrome treated with either clopidogrel or ticagrelor were included. Outcomes included first occurrence of death, MI, or stroke to indicate treatment effectiveness. A comparative effectiveness evaluation implementing six different study designs to adjusting for post-exposure treatment switching and censoring selection bias was conducted to compare to the PLATO RCT results. Marginal structural models were employed for multivariate confounding, time-dependent exposure, and censoring imbalance adjustments. The five analytical approaches were applied to the real-world data cohort included: intention-to-treat (ITT), as-treated (AT), time-dependent exposure (TD), intention-to-treat with censor-weighting (ITT-CW), and time-dependent exposure with censor-weighting (TD-CW).

Results: There were 146,310 individuals admitted to the hospital with ACS, of which, there were 12,992 (14%) initiated on clopidogrel and 1,557 (1.7%) initiated on ticagrelor. The ITT (HR: 0.92; 95%CI: 0.78-1.08) and AT (HR: 0.91; 95%CI: 0.76-1.10) analysis adjusting for time-fixed confounders derived similar point estimates with non-significant findings. The TD method (TD HR: 0.84; 95%CI: 0.71-1.0) adjusting for

time-fixed, time-varying exposure and time-varying confounding factors produced a point estimate consistent with the PLATO RCT.

Conclusions: The time-dependent exposure model (TD) produced results from the observational data that were close to the PLATO trial. Implementing weights that adjust for time-dependent exposure and time-dependent confounding factors can adequately account for the switching imbalance.

INTRODUCTION

Confounding and selection bias are key concerns that must be effectively addressed when conducting comparative effectiveness studies that utilize real-world data. Target trial emulation is the adaptation of randomized trial concepts to observational studies to improve study quality.[1] The active comparator, new user (ACNU) design and propensity score methods aim to mitigate bias resulting from the inability to randomize treatment exposure.[2] However, patient adherence to treatment in real-world settings is influenced by medication tolerability, adverse events, patient or prescriber preferences, and treatment effectiveness. Selection bias will be present if these factors precipitate differences in exposure patterns between comparators. For example, censoring patients based on differential consequences of treatment can bias results under the assumptions of many common analytic approaches.[3]

A lack of appreciation for selection bias in observational studies may be attributed to the following factors. Comparative effectiveness observational studies often employ an intention-to-treat (ITT) or a conventional as-treated (AT) analysis.[4] While each of these

approaches target different causal contrast, a tradeoff between clinical relevance and feasibility of obtaining unbiased estimates of the target parameter is made. The ITT approach requires the fewest assumptions evaluating the effect of initial treatment assignment but may not be the most clinically relevant analysis. Participants are followed from the time of treatment initiation (defined by the observational study) until preset criteria are reached; irrespective of treatment adherence, switching, or discontinuation.[5,6] In observational studies, treatment adherence is often omitted.[4] However, adherence should be evaluated and reported in any ITT analysis to add context for the interpretation of the effect estimates.[4] The traditional Cox model requires the assumption that censoring and events are conditionally independent given the covariates.[7] If the censored events are related to the outcome (conditional on being at risk, exposure, and baseline covariates) this assumption does not hold true and may invalidate results. In an AT analysis, only the person-time when patients are on treatment is evaluated. Patients with nonadherence are censored when deviation from initial exposure occurs.[5] The effect estimate will be biased if patients discontinue, switch, or are lost to follow-up for reasons related to treatment or outcome.[8,9] While methods for conducting analyses in the presence of informative censoring are not novel, censoring is often assumed to be non-differential and not assessed.

In this study, we examined the performance of different analytical approaches for addressing selection bias in the presence of differential treatment nonadherence in comparative effectiveness research (CER).[5] Under the ideal RCT scenario with perfect treatment adherence, any approach (ITT, AT, or per-protocol) would yield the same

effect estimate. We compared the effect estimates of various observational CER strategies, each with different levels of adjustment for confounding and treatment nonadherence, to a previously published RCT with negligible differences in protocol adherence between groups.

METHODS

Target Trial

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes (PLATO) was a double-blind, randomized, trial comparing ticagrelor versus clopidogrel for the prevention of cardiovascular events in patients admitted with an acute coronary syndrome (ACS). PLATO's purpose was to determine whether ticagrelor was superior to clopidogrel for the prevention of vascular events and death. In the primary ITT analysis, after 12-months of follow-up, the risk of the composite endpoint, all-cause death, myocardial infarction, or stroke was 16% lower in the ticagrelor group (HR: 0.84; 95%CI: 0.77-0.92, $p<0.001$). While there was no significant difference in the rates of major bleeding, ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting; including more instances of fatal intracranial bleeding. Patient adherence to assigned treatment was the same among groups (82.8%) with negligible differences in treatment discontinuation (23.4% vs 21.5%).

In order to empirically evaluate the performance of alternative methods for confounder adjustment, it was necessary to establish a reference-point or "working gold standard." Therefore, we constructed an empirical cohort to mimic the inclusion/exclusion criteria

for the PLATO trial, as closely as possible, using real world data. This performance evaluation was imperfect as we recognized that there are multiple reasons why the causal effect estimate from real-world data may not be identical to the RCT. However, it was the only feasible performance measurement that could be applied to empirical data.

Data Source

This study utilized the national Optum's de-identified Clinformatics® Data Mart Database (Optum Inc., Eden Prairie, MN) to conduct a retrospective cohort study. This database is a large, United States nationwide, managed care, administrative claims dataset comprised of longitudinal medical billing information. Insurance claims for all pharmacy, inpatient, and outpatient services are included for the enrolled 13 million yearly-members. Since this database does not capture over the counter (OTC) medication sales, we are not able to assess aspirin use within this population. This project achieved the determination of "research not involving human subjects" by the University of Rhode Island Institutional Review Board as all data were statistically de-identified prior to analyses.

Study Cohort

This study included patients aged 18 years or older with an ACS-related hospital admission between May 2012 and September 2015. This period was selected to align with the FDA approval of ticagrelor in July 2011 and delayed acceptance into the insurance formulary. Patients were required to have a hospital admission with a

diagnosis for an ACS treated with either clopidogrel or ticagrelor following discharge. ACS diagnosis 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]*). Patients were required to have at least 6 months of insurance eligibility prior to ACS hospitalization continuing until first pharmacy dispensing of study drug to evaluate baseline characteristics and exposure. At least one pharmacy prescription claim for either clopidogrel or ticagrelor within 14 days of discharge was required for inclusion. Patients with dispensings of P2Y12 antiplatelet agents, history of stroke, fibrinolytic therapy within one day of hospitalization, prior dispensings for oral anticoagulants, or dispensings of strong Cytochrome P-450 3A inhibitors/inducers identified during the baseline period were excluded. Additionally, patients with claims for more than one or non-study antiplatelet agent during the 14-day initiation window were excluded.

Outcomes Assessment

The primary outcome was defined as the first occurrence of one of any of the composite endpoints: 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 was included in these data, a day of death was randomly assigned within each month for death events occurring after hospital discharge. Myocardial infarctions and stroke events were identified by ICD-9-CM diagnosis codes (*MI: 410-412 [excluding 410.x2]; Stroke: 430-434, 436*) occurring

during inpatient hospitalization.[10,11] Patients were followed from ACS-hospital discharge until first endpoint occurrence, loss of insurance eligibility, or for 365 days; whichever occurred first. Because patients were initiated on antiplatelet therapy immediately and are often sent home with some hospital-dispensed days' supply, the follow-up period begins on the hospital discharge day instead of first outpatient prescription dispensing day.

Censoring Assessment

Censoring events were considered differently for each approach (specified below); but included insurance disenrollment, treatment switching, and treatment discontinuation. Insurance disenrollment was identified by eligibility end or a gap of 30 days or more in insurance enrollment. Treatment switching was identified via pharmacy claims as any prescription dispensing for an antiplatelet agent during the follow-up period in place of initial treatment. Patients were censored when switched to a non-study agent. Therapy discontinuation was defined as greater than 45 days of gap between prescription supply end and refill. To remain consistent with clinically appropriate treatment duration, gaps greater than 45 days occurring after 6-months of follow-up were not considered as discontinuation. Treatment adherence was calculated by a medication possession ratio of days' supply dispensed and days of follow-up. Patients with a medication possession ratio of greater than 80% were considered treatment adherent.

Covariates Assessment

Time-fixed 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-pump inhibitor, or diabetes medication use.[12,13]Angina and bleeding events requiring hospitalization, including gastrointestinal bleeding and major hemorrhage, were included as time-dependent covariates as they are potential indicators of inadequate or excessive platelet inhibition precipitating therapy switching.[14–16]

Statistical Analysis

Categorical variables are presented as frequencies (%) and compared using chi-square test. Continuous variables are presented as mean ± standard deviation (SD) and compared using student t-test. Marginal-structural models (MSM) were fit using inverse probability weights (IPW) to adjust for confounding. The robust variance estimator was utilized to account for the additional variability introduced by estimating the IPWs. Possible violations of positivity and misspecification was 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.[4] 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. Standardized differences in covariate means of ≤ 0.10 were assessed to indicated adequate balance after treatment weights were applied.

Time-Fixed Methods

In the time-fixed exposure approaches, the IPWs were derived by a ratio of the marginal probability of exposure and the probability of exposure given baseline covariates. The weights were used to create a pseudopopulation in which the measured covariates and treatment assignment were independent of each other.

Intention-To-Treat (ITT)

The intention-to-treat analysis in RCTs estimates the average causal effect of assigned treatment on the outcome. Whereby, all patients randomized to treatment are included in the analysis regardless of adherence to the randomized treatment. This method was adapted to our observational data by classifying patients to the treatment they initiated following the hospital discharge. Patients were censored if loss of follow-up due to insurance disenrollment but were not censored based on discontinuation, adherence, or switching.

As-treated (AT)

An as-treated analysis in RCTs classifies exposure based on the treatment a participant actually utilized, instead of following the randomized assignment.[14] The as-treated analysis estimates the effect of continuous use of the received initial study treatment throughout the follow-up. While there are many definitions for an as-treated analogue in observational studies, we classified patients to the treatment that was initially observed following hospital discharge.[17] Patients were censored when insurance

disenrollment, treatment discontinuation, or treatment switching occurred following initial exposure classification.

Time-Dependent Methods

Time-Dependent Exposure (TD)

The time-dependent weights were constructed to adjust for the previously mentioned fixed baseline and time-varying confounding factors.[18,19] Exposure was assessed at monthly intervals of prescription dispensings for each patient following initial assignment and continued until loss of eligibility, switching to non-study treatments, treatment discontinuation, event occurrence, or study end. The time-dependent variables were assessed during each month of follow-up. 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 history divided by the probability that the patient received the observed treatment given time, past treatment history, baseline covariates, and time-dependent factors.[20]

Censor Weighting (CW)

The censor-weighting approach accounted for measured imbalances due to informative censoring (e.g., insurance disenrollment, study end). These weights were estimated by a ratio of the probability of remaining enrolled in the insurance program for 12-months following index hospitalization given time and treatment during time interval divided by the conditional probability of remaining enrolled given time, treatment during time interval, baseline variables, and time-dependent confounding factors. The censor

weights were applied separately to the observational ITT (ITT-CW) and TD (TD-CW) analytic approaches to adjust for the difference in insurance disenrollment between treatment groups prior to follow-up end.

RESULTS

There were 146,310 individuals admitted to the hospital with ACS, of which, 71,287 (49%) had 6-months of insurance eligibility prior to index hospitalization and 44,338 (30%) of which were P2Y12-inhibitor new-users. After applying study exclusion criteria, there were 12,992 (14%) initiated on clopidogrel and 1,557 (1.7%) initiated on ticagrelor (Figure 1).

The clopidogrel group had higher rates of chronic kidney disease, anemia, chronic obstructive pulmonary disease, prior coronary artery bypass grafting, congestive heart failure, atrial fibrillation, β-blocker use, and diuretic use (Table 1). Patients initiated on clopidogrel had a higher rate of loss of insurance eligibility (41% vs. 37%, p=0.09), a lower rate of treatment switching (2% vs 18%, p<0.01), lower out of pocket costs ($9.78/month vs. $56.49/month, p=<0.01), and a longer average of days of follow-up (277 ±120 vs. 219 ±136, p<0.01). The rate of outcome events occurring after switching among the clopidogrel-to-ticagrelor switchers was much higher than the ticagrelor-to-clopidogrel switchers (C-T Switchers: 16.7% vs T-C Switchers: 4.6%).

The ITT (HR: 0.92; 95%CI: 0.78-1.08) and AT (HR: 0.91; 95%CI: 0.76-1.10) analysis adjusting for time-fixed confounders derived similar point estimates with non-

significant findings (Table 3). The TD method (TD HR: 0.84; 95%CI: 0.71-1.0) adjusting for time-fixed, time-varying exposure and time-varying confounding factors produced a point estimate consistent with the PLATO RCT (HR: 0.84; 95% CI: 0.77 – 0.92). Incorporating censor weights into the traditional ITT approach produced consistent results with the conventional methods (ITT-CW HR: 0.92; 95%CI: 0.78-1.09). Utilizing both the TD and CW weight approaches also derived an estimate consistent with the PLATO Trial (TD-CW HR: 0.83; 95%CI: 0.70-0.99).

DISCUSSION

In our observational study, patients assigned to the ticagrelor group switched treatment 9 times more frequently than the clopidogrel group (18% vs 2%, $p<0.01$). Because PLATO indicated that ticagrelor was superior to clopidogrel in preventing cardiovascular events in this setting, it is plausible that patients who escalated treatment from clopidogrel to ticagrelor may have done so for clinical reasons related to worsening of ischemic disease. The outcome event rate in the ticagrelor-clopidogrel switchers, occurring after switching, remained consistent with the rate observed in patients who were assigned to ticagrelor and did not switch (T-C Switchers Event Rate: 4.6% vs T Non-switchers: 4.5%). This is an indicator that people switching from ticagrelor to clopidogrel may be doing so for reasons unrelated to the outcome, such as cost or adverse effects of bleeding.

The outcome event rate in the clopidogrel-ticagrelor switchers, occurring after switching, was much higher than the patients who remained on clopidogrel (C-T

Switcher Event Rate: 16.7% vs C Non-Switchers: 5.9%). This is likely an indicator that escalating treatment from clopidogrel to ticagrelor reflects a higher risk of ischemic events. Methods that did not evaluate time-dependent confounding produced effect estimates closer to the null suggesting a more protective treatment effect of clopidogrel than what was observed in PLATO. Outcomes occurring after treatment switch were misclassified to initial exposure in a conventional ITT analysis and not counted when censored in the conventional AT analysis. As such, we found a negligible difference in the risk of outcome occurrence using ITT and AT analyses (ITT HR: 0.92, p=0.32; AT HR: 0.91, p=0.31).

Applying the censor weighting to the intention-to-treat (ITT-CW) analysis resulted in an effect estimate that was similar to the initial observational ITT analysis. The magnitude of the imbalanced loss to follow-up was not large enough to impact results (C: 37% vs T: 41%). We postulate that insurance disenrollment was not related to clinical events or measured confounding factors. Thus, the censor weight models could not adjust for this slight imbalance with the measured clinical confounders included. The time-dependent exposure model (TD) produced results from the observational data that were close to the PLATO Trial. Implementing weights that adjust for time-dependent exposure and time-dependent confounding factors can account for the switching imbalance.

Hernán and colleagues have written extensively on implementing the time-dependent analysis methods to real-world research. Hernán and Robins propose these methods to

improve the traditional per-protocol analyses by adjusting for confounding due to incomplete adherence to the assigned treatment. When discussing pragmatic trials, they note that adherence and loss to follow-up may be influenced by social and clinical factors occurring after randomization. Our data remained consistent with this idea as displayed by the switching imbalance observed between exposures. Failing to adjust for post-assignment factors can impose confounding and selection bias in some scenarios. After we adjusted for time-dependent confounding and treatment, our observational results were consistent with PLATO — where this source of bias was minimized.

LIMITATIONS

First, exact replication of the clinical trial population was not possible with this data source. Some of the clinical trial inclusion/exclusion criteria were based on laboratory values (e.g., electrocardiography, myocardial necrosis indicators, creatinine clearance, and percent of vascular occlusion) and were measured as a part of PLATO enrollment. Since the laboratory data is limited within the administrative data, these components of the RCT inclusion criteria could not be applied toto our study cohort selection. Second, this study could not account for over the counter (OTC) medication utilization, such as aspirin. Aspirin is a fundamental aspect of dual-antiplatelet therapy and its utilization cannot be measured. Similarly, some non-steroidal anti-inflammatory drugs and proton-pump inhibitors are also classified as OTC and the potential effects of these agents on cardiovascular outcomes or drug-drug interactions could be underestimated. Third, this study could not evaluate information regarding type of stent, antiplatelet loading-dose, or other particular details of inpatient procedures as such information was not included

within the data. Fourth, since 2013 it was no longer mandatory for states to report death events to the Social Security Administration.[21] As such, deaths occurring after 2013 are underreported as the Optum Clinformatics™ Data Mart utilizes the Social Security Administration Death Master File as the source for date of death. Additional limitations regarding this data set include generalizability to low income or age 65+ individuals as only a portion of these patients are included within this database. Last, 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 the observational setting; however, we relied on comprehensive literature review and clinical expertise to bolster this assumption. We also assumed that the models implemented were correctly 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

Real-world treatment regimens are not static and will change over time in accordance with clinical prognosis, patient and provider preferences, treatment tolerance, and non-clinical factors (cost, insurance coverage, etc.). To answer causal questions on the effects of non-static treatment regimens, it is imperative to fully evaluate and adjust for treatment nonadherence.

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Figure 1. Study Population

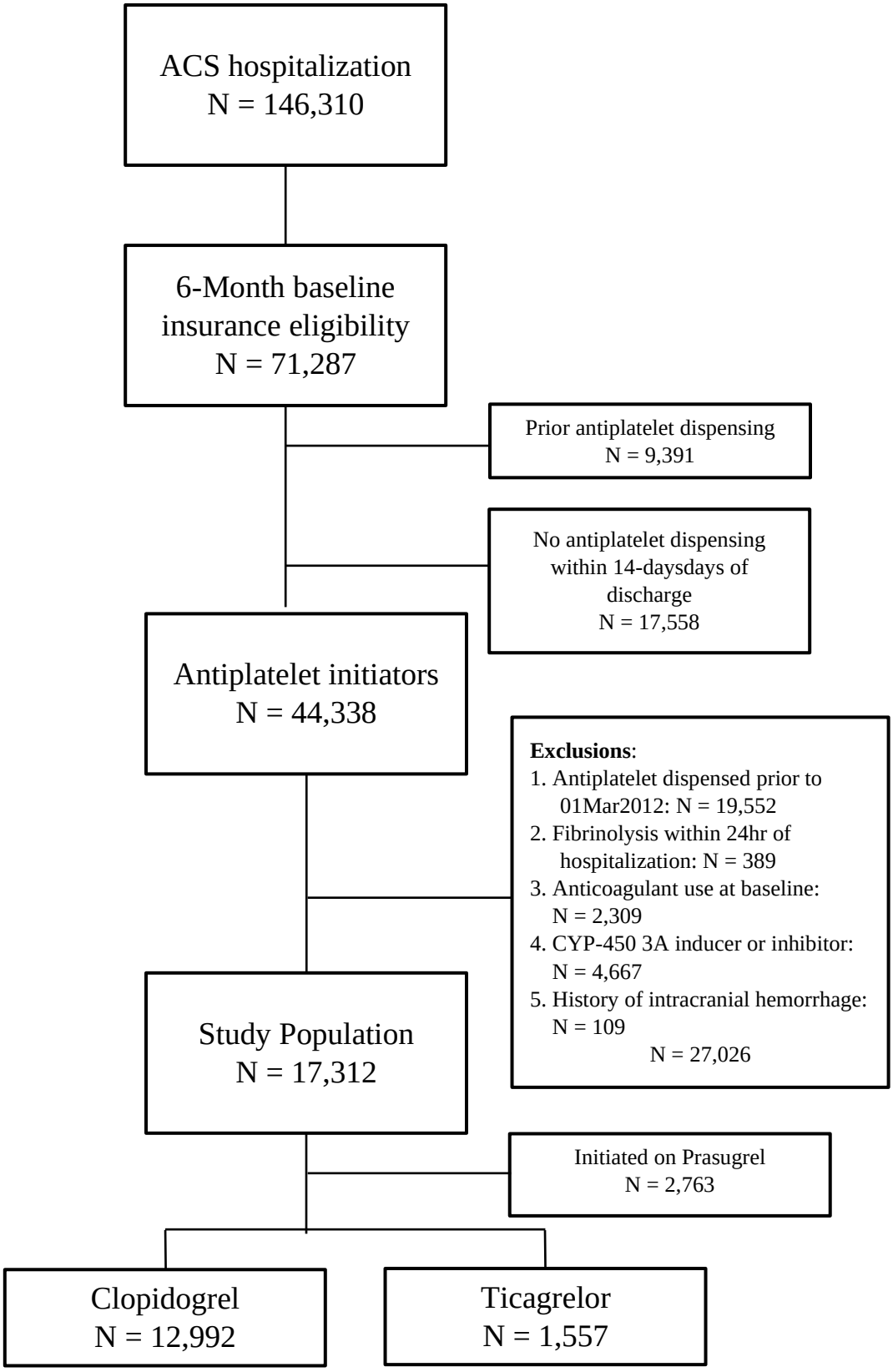
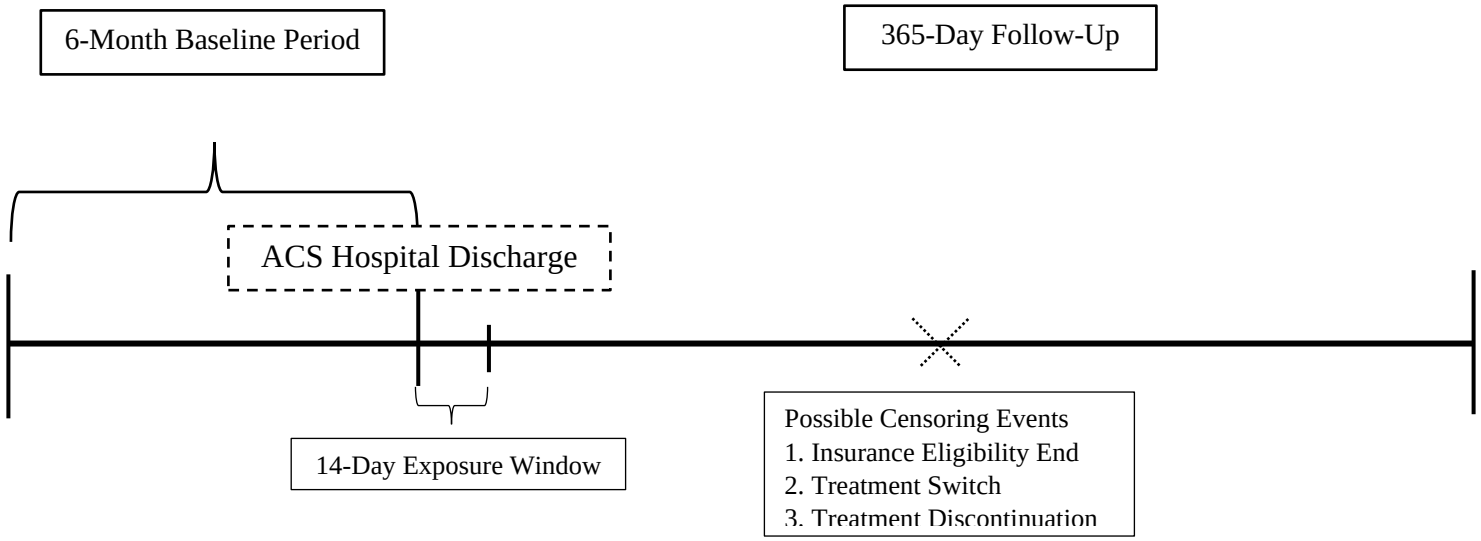


Figure 2. Study Design Schematic



Study Designs:
1. Intention-to-Treat (ITT) – Exposure: Initial Treatment, Censored: LOE
2. As-Treated (AT) – Exposure: Initial Treatment, Censored: LOE, Treatment Switch, Treatment Discontinuation
3. Censoring Weighted Intention-to-Treat (ITT-CW) – Exposure: Initial Treatment, Censored: Weighted by MOE
4. Time-Dependent (TD) – Exposure: Monthly Treatment, Censor: LOE, Switch to Prasugrel
5. Time-Dependent Censoring Weighted (TD-CW) – Exposure: Monthly Evaluation, Censored: Weighted by MOE, Switch to Prasugrel

LOE: Loss of Insurance Eligibility, Prasugrel: Switching to Prasugrel, MOE: Number of months of follow-up insurance eligibility

Table 1. Baseline Demographic and Comorbidities by Initial Exposure

Characteristics	Clopidogrel (%) n = 12,992		Ticagrelor (%) n = 1,557		P
Age (±SD)	65.8	±12	64.2	±12	0.53
Female	4,205	(32)	449	(29)	<0.01
Tobacco	3,126	(24)	386	(25)	0.52
Hypertension	9,931	(76)	1,166	(75)	0.18
Hyperlipidemia	9,117	(70)	1,119	(72)	0.17
Carotid Artery Stenosis	4,837	(37)	549	(35)	0.13
Chronic Kidney Disease	1,248	(10)	110	(7)	<0.01
Anemia	1,463	(11)	143	(9)	0.01
COPD	2,156	(17)	218	(14)	<0.01
Asthma	726	(6)	74	(5)	0.17
PTCA	1,005	(8)	128	(8)	0.50
CABG	699	(5)	62	(4)	0.02
Congestive Heart Failure	2,513	(19)	268	(17)	0.04
Atrial Fibrillation	1,175	(9)	106	(7)	<0.01
ACE/ARB	4,810	(37)	556	(36)	0.31
Beta-Blocker	3,717	(29)	386	(25)	<0.01
Diuretic	2,179	(17)	203	(13)	<0.01
Statin	4,592	(35)	516	(33)	0.09
Diabetes Med	2,951	(23)	347	(22)	0.70
Proton-Pump Inhibitor	2,202	(17)	248	(16)	0.31
Calcium Channel Blocker	445	(3)	46	(3)	0.4

Note: Chronic Obstructive Pulmonary Disease (COPD), Percutaneous Transluminal Coronary Angioplasty (PTCA), Coronary Artery Bypass Grafting (CABG), Angiotensin-Converting Enzyme/Angiotensin Receptor Blocker

Table 2. Comparing Raw Outcome Frequencies by Initial Exposure

Outcomes	**Clopidogrel (%)**		**Ticagrelor (%)**		**P Value**
	n =	15,953	n =	2,262	
All-cause Death	321	(2)	22	(1)	<0.01
Myocardial Infarction	727	(5)	91	(4)	0.25
Ischemic Stroke	179	(1)	24	(1)	0.79
Composite Outcome	932	(6)	109	(5)	0.05

Table 3. Model Results by Analysis Methods

Model	Adjusted Hazard Ratio	95% Confidence Interval		P-Value
Unadjusted	0.80	0.58	1.10	0.15
ITT	0.92	0.78	1.08	0.32
AT	0.91	0.76	1.10	0.31
ITT-CW	0.92	0.78	1.09	0.33
TD	0.84	0.71	1.00	0.06
TD-CW	0.83	0.70	0.99	0.04
PLATO Trial	0.84	0.77	0.92	<0.01

Note: Intention-to-treat (ITT), As-treated (AT), Intention-to-treat with censor weighting (ITT-CW), Time-dependent exposure (TD), Time-dependent exposure with censor weighting (TD-CW)

Table 4. Standardized Differences of Baseline Covariates between Two Comparison Groups by Analysis Methods

Baseline Characteristics	Crude	ITT	AT	ITT-CW	TD	TD-CW
Female	0.18	<0.01	0.02	0.05	0.06	0.06
Tobacco	0.05	<0.01	<0.01	0.03	0.02	0.02
Hypertension	0.07	<0.01	0.01	0.02	0.03	0.04
Hyperlipidemia	0.01	<0.01	0.02	0.02	0.02	0.02
Carotid Artery Stenosis	0.04	<0.01	0.01	<0.01	0.02	0.02
Peripheral Vascular Disease	0.07	<0.01	<0.01	0.04	0.05	0.05
Chronic Kidney Disease	0.08	<0.01	0.01	0.01	0.05	0.06
Dialysis	0.12	0.01	0.02	0.05	0.05	0.09
Anemia	0.06	<0.01	0.02	0.02	0.03	0.04
COPD	0.06	<0.01	<0.01	0.03	0.07	0.07
Asthma	0.12	<0.01	0.01	0.02	0.09	0.09
PTCA	0.05	0.01	0.02	0.03	0.02	0.03
CABG	0.01	<0.01	<0.01	0.02	0.01	0.02
Congestive Heart Failure	0.17	0.01	0.01	0.01	0.09	0.09
Atrial Fibrillation	0.08	<0.01	0.01	0.03	0.04	0.05
ACE/ARB	0.08	<0.01	0.01	0.02	0.07	0.08
Beta-Blocker	0.08	<0.01	0.02	0.02	0.03	0.05
Diuretic	0.18	0.01	0.01	0.06	0.09	0.12
Statin	0.11	<0.01	<0.01	0.04	0.06	0.07
Diabetes Med	0.07	<0.01	0.01	0.01	0.02	0.04
Proton-Pump Inhibitor	0.02	<0.01	0.01	0.01	<0.01	0.01

Note: Intention-to-treat (ITT), As-treated (AT), Intention-to-treat with censor weighting (ITT-CW), Time-dependent exposure (TD), Time-dependent exposure with censor weighting (TD-CW), Chronic Obstructive Pulmonary Disease (COPD), Percutaneous Transluminal Coronary Angioplasty (PTCA), Coronary Artery Bypass Grafting (CABG), Angiotensin-Converting Enzyme/Angiotensin Receptor Blocker

Table 5. Distributions of Estimated Stabilized Weights by Analysis Methods

Percentile	**ITT**	**AT**	**TD**	**ITT-CW**	**TD-CW**
100% Max	1.05	1.05	1.24	1.15	1.27
99%	1.03	1.03	1.10	1.07	1.09
95%	1.03	1.03	1.00	1.04	1.04
90%	1.02	1.02	1.00	1.02	1.02
75% Q3	1.01	1.01	1.00	1.01	1.00
50% Median	1.00	1.00	1.00	1.00	0.99
25% Q1	0.99	0.99	1.00	0.98	0.97
10%	0.97	0.97	1.00	0.96	0.95
5%	0.96	0.96	1.00	0.95	0.94
1%	0.95	0.95	0.94	0.93	0.92
0% Min	0.92	0.92	0.52	0.89	0.74
Mean	1.00	1.00	1.00	0.99	0.99

Note: Intention-to-treat (ITT), As-treated (AT), Intention-to-treat with censor weighting (ITT-CW), Time-dependent exposure (TD), Time-dependent exposure with censor weighting (TD-CW)

MANUSCRIPT II

Title: **The Comparative Effectiveness and Safety of Prasugrel versus Ticagrelor following Percutaneous Coronary Intervention**

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This project has not yet been submitted for publishing.

ABSTRACT

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 Clinformatics Datamart and included patients aged 18 years or older with an index hospital admission between May 2012 and December 2015, a diagnosis acute coronary syndrome managed with percutaneous coronary intervention, and those treated with either ticagrelor or prasugrel. The primary outcome was defined as the first occurrence of one of any of the composite endpoints: all-cause death, myocardial infarction, or ischemic stroke. The secondary outcome was defined as the first occurrence of the composite endpoints: 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: There were 2,559 (3%) initiated on ticagrelor and 4,456 (5%) initiated on prasugrel following PCI. Patients initiated on ticagrelor had a 10% higher rate of eligibility disenrollment and a 7% higher rate of medication switching. After adjusting for multiple confounding factors, time-varying exposure, and censoring imbalance, ticagrelor was associated with a higher risk in all-cause death, MI, and stroke when compared to prasugrel (HR: 1.33; 95%CI: 1.04-1.68; p=0.02). Similarly, ticagrelor was associated with a higher risk in bleeding events (HR: 1.61; 95%CI: 1.19-2.17; p<0.01).

Conclusion: After adjusting for multiple confounding factors, time-varying exposure, and censoring imbalance, prasugrel showed a lower risk in death, MI, and stroke when compared to ticagrelor. Similarly, prasugrel was associated with a reduced risk in bleeding events.

INTRODUCTION

Dual antiplatelet therapy (DAPT), consisting of aspirin plus a P2Y12 agent, in patients treated with percutaneous coronary intervention (PCI) reduces the risk of subsequent ischemic events and has remained a mainstay in treatment for two decades.[1–3] *The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5* trail was a randomized, open-label study evaluating ticagrelor versus prasugrel in patients with acute coronary syndromes (ACS) concluded that ticagrelor had significantly higher rates in the incidence of death, myocardial infarction, or stroke.[4] These findings were unexpected as the authors hypothesized that ticagrelor would be superior to prasugrel. Observational studies addressing the head-to-head comparison of ticagrelor and prasugrel have contradictory results. Dawwas et al. evaluated the comparative effectiveness and safety of ticagrelor versus prasugrel in patients with ACS.[5] Their results indicated that ticagrelor was associated with a decreased risk of recurrent nonfatal CVD events and major bleeding events. 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.[6] However, most observational studies find no significant

difference between ticagrelor and prasugrel users in adverse cardiovascular and bleeding events.[7–11] These observational studies did not mention the rate of censoring between exposure groups. While patients were censored if treatment switching or insurance disenrollment/dropout occur, censoring was assumed to be non-differential and negligible between groups even without evaluating these rates.[12] Real-world data requires a thorough evaluation of the independent censoring assumption to avoid post-treatment bias and confounding by time dependent confounding factors.

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. We implemented marginal structural models and inverse probability censoring weighting to adjust for post-treatment selection bias caused by imbalance in treatment 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 obtain results similar to the ISAR-REACT 5 trial.

METHODS

Data Sources

We utilized the national Optum's de-identified Clinformatics® Data Mart Database (Optum Inc., Eden Prairie, MN) to conduct a retrospective cohort study. This database is a large, United States nationwide, managed care, administrative claims dataset comprised of longitudinal medical billing information. Insurance claims for all

pharmacy, inpatient, and outpatient services are included for the enrolled 13 million yearly-members.[13] This project achieved the determination of "research not involving human subjects" by the University of Rhode Island Institutional Review Board as all data were statistically de-identified prior to analyses.

Definition of Study Cohort

Patients aged 18 years or older with a hospital admission between May 2012 and December 2015 and 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 and delayed acceptance into the insurance formulary. ACS diagnosis 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]*).[14] 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*) occurring during the hospitalization attributed to the ACS event.[11] At least one pharmacy prescription claim for either ticagrelor or prasugrel within 14 days of discharge was required for inclusion.[11] Patients with dispensings of ticagrelor or prasugrel, history of stroke, fibrinolytic therapy within one day of hospitalization, prior dispensings for oral anticoagulants, or dispensings of strong Cytochrome P-450 3A inhibitors/inducers identified during the baseline period were excluded.[4,15] 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 outcome was defined as the first occurrence of one of any of the composite endpoints: 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 was included in these data, a day of death was randomly assigned within each month for death events occurring after hospital discharge. Myocardial infarctions and stroke events were identified by ICD-9-CM diagnosis codes (*MI: 410-412 [excluding 410.x2]; Stroke: 430-434, 436*) occurring during inpatient hospitalization.[16,17] The secondary outcome was defined as the first occurrence of the composite endpoints: gastrointestinal bleed, intracranial hemorrhage, or other major bleeds requiring hospitalization.[18] Patients were followed from PCI-hospital discharge until first endpoint occurrence, loss of insurance eligibility, or for 365 days; whichever occurred first.

Censoring Assessment

Censoring events included insurance disenrollment, treatment switching, and treatment discontinuation. 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 assigned agent and subsequent replacement of an alternative agent, as identified via prescription pharmacy claims. Patients were censored when switched to a non-study agent (i.e. clopidogrel). Therapy discontinuation was defined as a greater than 45 days of gap between prescription supply end and refill. Since treatment duration of 6 to 12 months is recommended in this setting, gaps greater

than 45 days occurring after 6-months of follow-up were not considered as discontinuation.[19]

Covariates 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-pump inhibitor, or diabetes medication use.[19,20] Angina, prior interval treatment, and 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 test. Continuous variables are presented as mean ± standard deviation (SD) and compared using student t-test. Marginal-structural models (MSM) were fit using inverse probability weights (IPW) to adjust for confounding with time-dependent variables.[21,22] Possible violations of positivity and misspecification was 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.[23] 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.[24,25] 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 baseline and time-varying confounding factors. Exposure was assessed at monthly intervals of prescription dispensings for each patient following initial assignment and continued until loss of eligibility, switching to non-study treatments, 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.[26]

Censoring Weighting (CW)

The censor-weighting accounted for possible informative censoring (e.g., insurance disenrollment) due to measured confounding factors. These weights were estimated by a ratio of the probability of remaining enrolled in the insurance program for 12-months following index hospitalization given time, prior treatment divided by the conditional probability of remaining enrolled given time, prior treatment, baseline variables, and time-dependent confounding factors.[26,27] 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 remain consistent with the approaches used in previously published observational studies. Patients were censored 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.[28] 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 the clopidogrel exposure during baseline period impacts conclusions, we narrowed the population to antiplatelet-naïve patients by excluding those with clopidogrel exposure during the baseline period. While the ISAR-REACT 5 trial allowed patients with a history of clopidogrel use to enroll, we hypothesized that the results would not be different in a completely P2Y12-antiplatelet naïve population.

RESULTS

Study Population

There were 91,682 individuals admitted to the hospital with an acute coronary syndrome who underwent percutaneous coronary intervention during a hospitalization for an acute coronary syndrome. Only 71,287 (78%) had 6-months of insurance eligibility prior to index hospitalization. After applying the exclusion criteria, there were 2,559 (3%) initiated on ticagrelor and 4,456 (5%) initiated on prasugrel following PCI (Figure 1).

The ticagrelor group had significantly higher rates of comorbidities at baseline (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 had a 10% higher rate of eligibility disenrollment and a 7% higher rate of medication switching (Table 2). The ticagrelor group had a 2% higher frequency of prior clopidogrel users compared to the prasugrel group. Treatment discontinuation was balanced between groups.

Comparative Effectiveness Results

The composite outcome death, myocardial infarction, and ischemic stroke occurred more frequently in the ticagrelor group (Table 3). Gastrointestinal bleeding, intracranial hemorrhage, and other major bleeding requiring hospitalization were also more frequent in the ticagrelor group, although neither were statistically significant. After adjusting for multiple confounding factors, time-varying exposure, and censoring imbalance, ticagrelor was associated with a higher risk in all-cause death, MI, and stroke when compared to prasugrel (HR: 1.33; 95%CI: 1.04-1.68; p=0.02) (Table 4). Similarly,

ticagrelor was associated with a higher risk in bleeding events (HR: 1.61; 95%CI: 1.19-2.17; p<0.01).

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. The ITT approach associated ticagrelor with a lower rate of all-cause death, MI, and stroke (HR: 0.78; 95%CI: 0.58-1.06; p=0.11) and lower risk in bleeding events (HR: 0.84; 95%CI: 0.58-1.20, p=0.33), although these results were non-significant.

Clopidogrel Naïve Population

Results were similar to the original study population (where prior clopidogrel use was allowed). The TD-CW method for primary (HR: 1.28; 95%CI: 0.99-1.66; p=0.06) and secondary (HR: 1.63; 95%CI: 1.19-2.23, p<0.01) composite outcomes remained consistent. Similarly, ITT results for the primary (HR: 0.81; 95%CI: 0.59-1.11; p=0.19) and secondary (HR: 1.05; 95%CI: 0.73-1.51; p=0.79) were consistent with the original population with less precision.

DISCUSSION

This study was consistent with the ISAR-REACT 5 trial that showed that prasugrel was associated with a lower risk of ischemic and bleeding events in patients treated for ACS. While treatment guidelines recommend prescribing prasugrel and ticagrelor with equal

affinity following PCI, many factors can influence treatment selection potentially explaining the observed imbalances between disenrollment or antiplatelet switching.[19,29] While most observational studies 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. Utilizing this approach produced results consistent with the ISAR-REACT 5 trial with a cohort where dropout and treatment switching rates between randomized groups were negligible.

The observational literature about outcomes of antiplatelet use have competing results.[5,7–11,20] Variability in follow-up time, study approaches, and assumptions contribute to a breadth of conclusions. It is not appropriate to implement a conventional ITT analytic approach when censoring events are imbalanced between treatment groups and differential censoring is present. Our ITT sensitivity analysis provided results that were consistent with recent observational studies evaluating these agents and contrary to the ISAR-REACT 5 trial. It was evident that ignoring differential post-assignment imbalances between exposure groups can produce results in the opposite direction and may contribute to the variability of results in observational studies.

While there was a statistically significant 2% higher rate in clopidogrel exposure identified during the baseline period of the ticagrelor group, narrowing the population to antiplatelet-naïve patients by excluding those with prior clopidogrel exposure produced results similar to the standard population with a slight loss in power. This

indicated that clopidogrel use during the baseline period did not impact the estimated treatment effect.

LIMITATIONS

First, the balance between ischemic and bleeding risk plays an integral role in treatment selection. As this evaluation is conducted by the clinician on a patient-by-patient basis, misclassification, under reporting, or events occurring greater than 6-months in the past were not incorporated into the treatment weights. Second, this study could not account for over-the-counter (OTC) medication utilization, such as aspirin. Aspirin is a fundamental aspect of dual-antiplatelet therapy and its utilization cannot be measured. Similarly, some non-steroidal anti-inflammatory drugs and proton-pump inhibitors are also classified as OTC and the potential effects of these agents on cardiovascular outcomes or drug-drug interactions could be underestimated. Third, this study could not evaluate information regarding type of stent, antiplatelet loading-dose, or other details of inpatient procedures as such information was not included within the data. Fourth, since 2013 it was no longer mandatory for states to report death events to the Social Security Administration.[30] As such, deaths occurring after 2013 are underreported as the Optum Clinformatics™ Data Mart utilizes the Social Security Administration Death Master File as the source for date of death. Additional limitations regarding this data set include generalizability to low income or age 65+ individuals as only a portion of these patients are included within this database. Last, 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 the observational setting; however, we relied on comprehensive literature review and clinical expertise to bolster this assumption. We also assumed that the models implemented were correctly 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

Marginal structural models with IPTW and IPCW were utilized to adjust for imbalances in post-exposure variables, in addition to baseline confounders, that would have imposed a differential and dependent censoring. After adjusting for multiple confounding factors, time-varying exposure, and censoring imbalance, prasugrel showed a lower risk in death, MI, and stroke when compared to ticagrelor. Similarly, prasugrel was associated with a reduced risk in bleeding events.

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Figure 1. Study Population

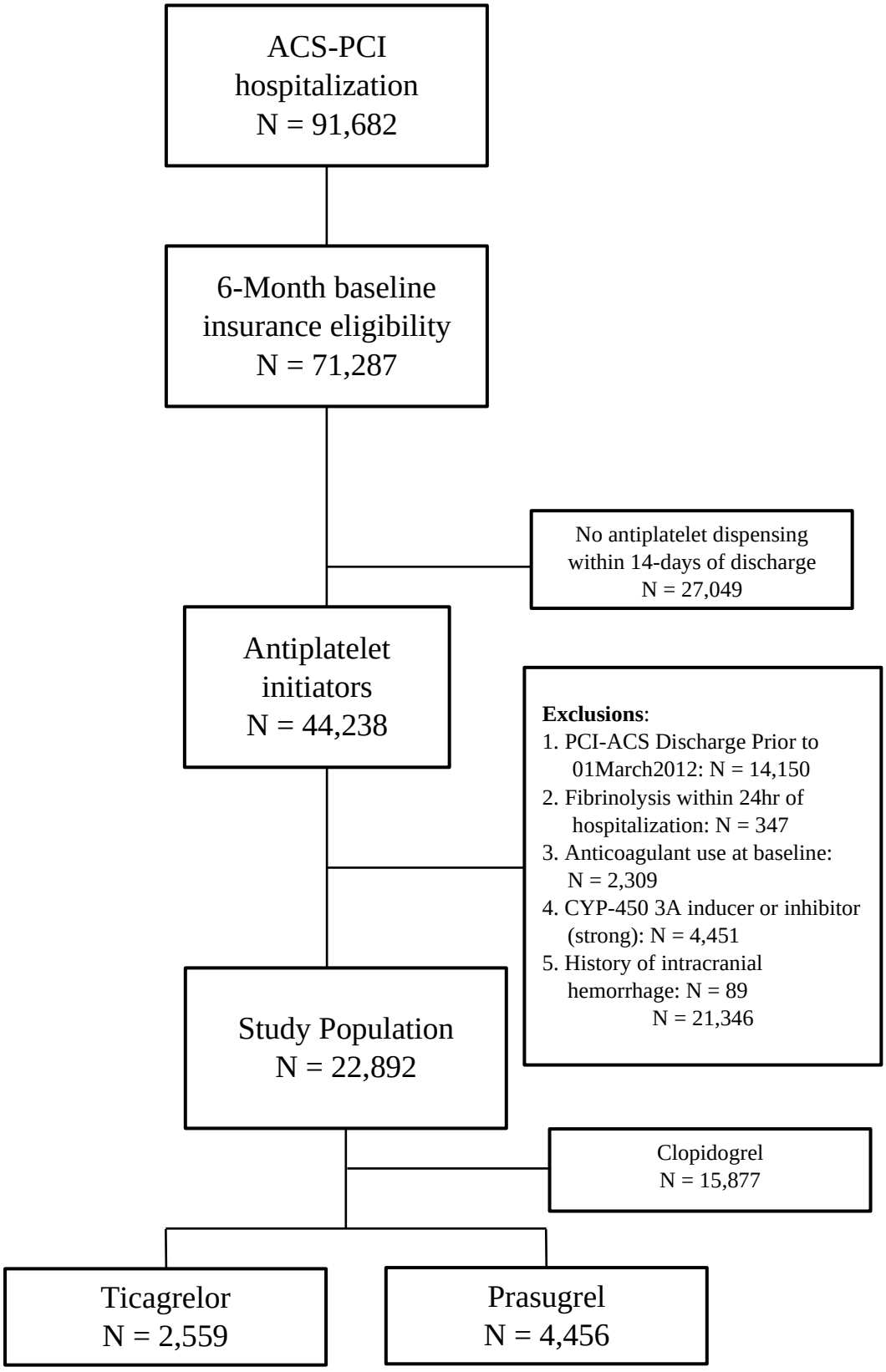


Table 1. Baseline Characteristics by Initial Exposure

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

Table 2. Censoring Frequencies by Initial Exposure

Censoring Criterion	Ticagrelor (%) n = 2,639		Prasugrel (%) n = 4,566		P Value
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

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

Outcomes	**Ticagrelor (%)** n =2,639		**Prasugrel (%)** n = 4,566		**P value**
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
Composite Outcome	119	(4.5)	172	(3.8)	0.12
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
Composite outcome	72	(2.7)	98	(2.1)	0.12

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

Time-Dependent Censor-Weighted (TD-CW)	**HR**	**95% Cl**		**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)

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

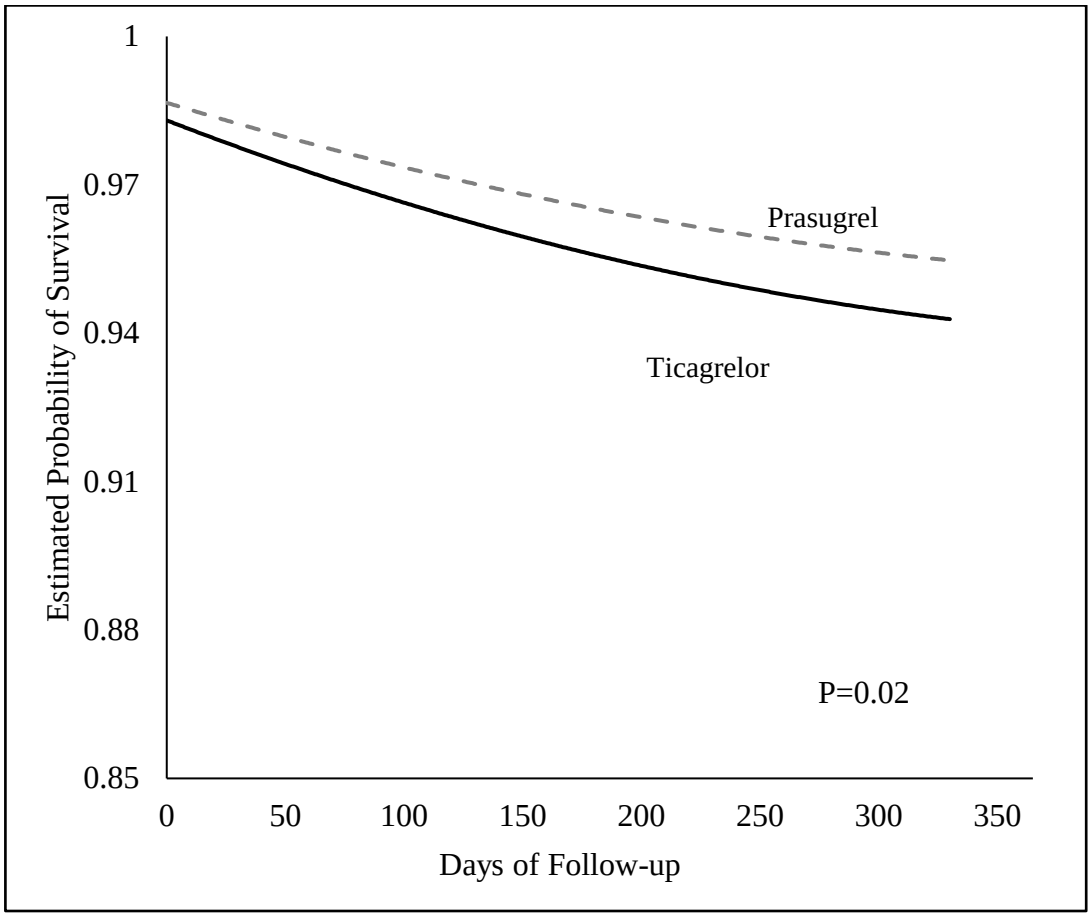
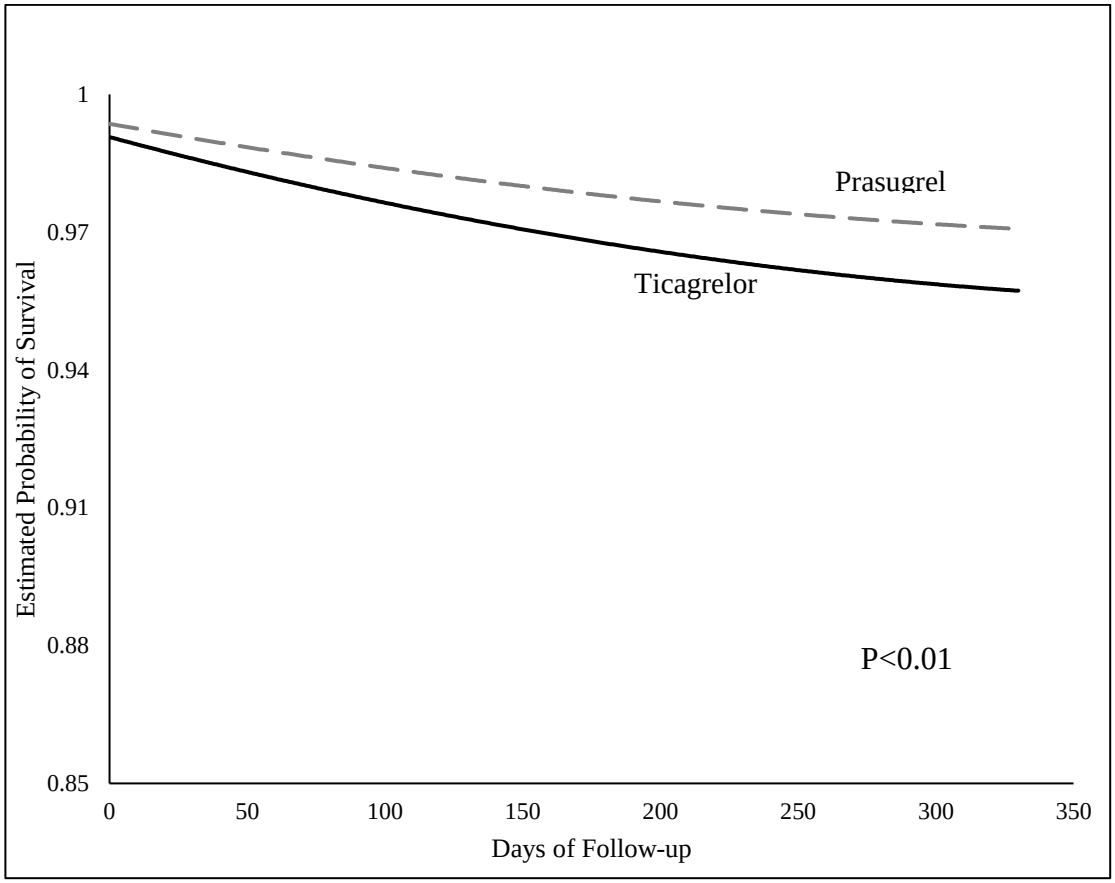


Figure 3. Estimated survival curve for gastrointestinal (GI) bleed, intracranial hemorrhage (ICH), or other major bleed requiring hospitalization in weighted pseudopopulation



MANUSCRIPT III

Title: **Costs and Healthcare Resource Utilization of Antiplatelet Escalation following Acute Coronary Syndromes**

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This project has not yet been submitted for publishing.

ABSTRACT

Background: For patients with an acute coronary syndrome (ACS) treated with clopidogrel, switching to ticagrelor or prasugrel represents a clinical treatment escalation. There is a lack of research evaluating the costs and frequency of healthcare encounters associated with this treatment escalation.

Objectives: To compare the direct drug and health system costs and healthcare resource utilization (HRU) associated with escalating from clopidogrel, to either ticagrelor or prasugrel following an ACS.

Methods: This retrospective cohort study used the Optum ClinformaticsTM database to study patients that escalated antiplatelet therapy following an ACS from 2012 to 2015. Patients were followed for up to 12-months following date of switch from clopidogrel, until insurance disenrollment, or death. Median per-patient per-month (PPPM) all-cause and cardiovascular-related (CV) charges and healthcare utilization were evaluated for each patient following escalation. CV medical encounter cost included subsequent ACS, revascularization, or stroke events. CV prescription costs included charges attributed to beta-blockers, ACE/ARBS, diuretics, antiarrhythmics, statins, fibric acid derivatives, bile acid sequestrants, calcium channel blockers, and anticoagulants. Propensity-score (PS) 1:1 greedy matching was used to adjust for confounders. All cause and CV charges, and frequencies of HRU were compared between the two PS-matched groups of ticagrelor and prasugrel escalators. To assess the effect of treatment escalation on costs and healthcare resource utilization generalized linear models were fitted using a log-link function with gamma distribution or lognormal distribution, depending on the outcome of interest.

Results: There were 21,103 (23%) patients initiated on clopidogrel, 5,040 (6%) initiated on prasugrel, and 2,974 (3%) initiated on ticagrelor lowing PCI. Of the clopidogrel initiators, 132 switched to ticagrelor and 281 switched to prasugrel within 1 year of initial therapy. Patients who escalated to ticagrelor experienced 33% lower all-cause costs (RR: 0.67, 95%CI: 0.44-0.99, p=0.05) when compared to those switching to prasugrel. There was no significant difference found in all-cause outpatient (RR: 0.94, 95%CI: 0.60-1.48, p=0.80), hospitalizations (RR: 0.58, 95%CI: 0.31-1.07, p=0.08), or prescription (RR: 0.82, 95%CI: 0.64-1.05, p=0.12) costs. : 0.58, 95%CI: 0.31-1.07, p=0.08), or prescription (RR: 0.82, 95%CI: 0.64-1.05, p=0.12) costs. The ticagrelor escalators also experienced 49% lower CV-related total costs (RR: 0.51, 95%CI: 0.33-0.76, p<0.01) driven by the 61% lower CV inpatient costs (RR: 0.39, 95%CI: 0.16-0.96, p=0.04).

Conclusion: We found that patients escalating antiplatelet therapy from clopidogrel to ticagrelor were associated with less total all-cause costs and total cardiovascular-related costs driven by lower cardiovascular-related hospitalization costs when compared to patients escalating to prasugrel

INTRODUCTION

Dual antiplatelet therapy, consisting of an oral P2Y12-inhibitor and aspirin, is the standard of care for the preventing ischemic events in patients with acute coronary syndrome (ACS).[1,2] Pharmacodynamic and randomized controlled trials show that ticagrelor and prasugrel are associated with enhanced antiplatelet effects and reduced ischemic outcomes when compared to clopidogrel.[3,4] Even though clopidogrel and prasugrel are both thienopyridines, prodrugs that rely on first pass metabolism for conversion into their active forms and bind to the same location on the P2Y12 receptor, prasugrel activation is less dependent on hepatic metabolism resulting in a more potent and consistent inhibition of platelets.[5] Ticagrelor, a triazolopyrimidine, does not require first-pass activation, binds to a different site on the P2Y12-receptor, and is readily absorbed. Switching between different oral P2Y12-inhibitors after being treated on an initial agent can occur in an effort to leverage these differences in pharmacodynamic activity to improve subsequent clinical outcomes.

Switching to ticagrelor or prasugrel can indicate an escalation in therapy and is an option in patients who have an ACS event while already being treated with clopidogrel.[6] However, there is limited research regarding the clinical and economic outcomes related to this type of switch as patients with prior P2Y12-inhibitor treatment are often excluded from analyses.[7] Registry studies indicate that the prevalence of escalating from clopidogrel is between 5-50% depending on the clinical setting, but were not designed to assess clinical outcomes.[8–10] All pharmacodynamic studies have shown increased platelet inhibition when escalating from clopidogrel to either ticagrelor or prasugrel,

however there have been no studies evaluating costs and healthcare resource utilization (HRU) associated with this therapy change.[11–14] There have been several studies comparing costs between patients who are treated with antiplatelet agents following ACS, but none evaluating those that escalate therapy.[15–18] The most recent compared 6-month costs between all oral antiplatelet agents following acute coronary syndromes and did not find significant differences between ticagrelor and prasugrel in costs but higher HRU in ticagrelor patients. Our objective was to compare the direct health system costs and healthcare resource utilization associated with escalating to either ticagrelor or prasugrel following initial clopidogrel treatment due to an ACS event. We aimed to determine if the pharmacodynamic differences between ticagrelor and prasugrel translate to differences in costs or HRU and if escalating to one agent is more advantageous than the other.

METHODS

Data Sources

This study utilized the national Optum's de-identified Clinformatics® Data Mart Database (Optum Inc., Eden Prairie, MN) to conduct a retrospective cohort study. This database is a large, United States nationwide, managed care, administrative claims dataset comprised of longitudinal medical billing information. Insurance claims for all pharmacy, inpatient, and outpatient services are included for the enrolled 13 million yearly-members.[19] Mortality was identified from the Social Security Death Index dataset. This project achieved the determination of "research not involving human

subjects" by the University of Rhode Island Institutional Review Board as all data were statistically de-identified prior to analyses.

Definition of Study Cohort

The study included patients aged 18 years or older with a hospital admission between January 2012 and September 2015 and a diagnosis of ACS treated with clopidogrel. ACS diagnosis 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]*).[20] Patients with their first outpatient prescription dispensing of an antiplatelet agent within 14 days of discharge for clopidogrel were included. Patients that permanently switched to either ticagrelor or prasugrel at any point, defined by pharmacy claims where clopidogrel dispensings were discontinued and replaced with the study treatments, were included. Patients that remained on clopidogrel for the duration of treatment were not evaluated in this study. At least one year of continuous insurance eligibility, with at least 6-months of eligibility prior to index ACS hospitalization, were required for inclusion. Patients were followed for up to 12-months following date of switch from clopidogrel, until insurance disenrollment, or death.

Baseline Confounders

Comorbidities were assessed using diagnosis codes queried within inpatient and outpatient medical claims during the 6-months baseline period occurring prior to the index hospitalization. Comorbidities 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. Medication utilization including beta-blocker, diuretic, statin, proton-pump inhibitor, or diabetes therapies during the baseline period were assessed using outpatient pharmacy claims.[1,21] Inpatient medications and over-the-counter medications not covered by insurance were not available in this dataset.

Charges and Healthcare Resource Utilization

All-cause and disease-related charges and healthcare utilization were evaluated for patients that escalated antiplatelet therapy by switching from clopidogrel to either ticagrelor or prasugrel. All-cause charges were calculated by aggregating total outpatient, inpatient, and prescription costs for any encounter or medication. All-cause healthcare resource utilization was calculated as a summation of all inpatient or outpatient medical encounters occurring on different days or different hospitalizations. Cardiovascular-related charges and HRU were similarly calculated but were identified with a diagnosis codes for myocardial infarction, stroke, PCI, or other ACS events.[22] Charges for prescription cardiovascular medications included: anticoagulants, antiplatelet agents, ACE inhibitors, angiotensin II receptor blockers, beta blockers, calcium channel blockers, cholesterol lowering medications, digitalis preparations, diuretics, and vasodilators were aggregated.[23] All charges were adjusted to 2019 $US equivalents using the annual medical care component of the Consumer Price Index.[24] All charges and medical encounter frequencies were converted to a per-patient per-

month (PPPM) amount based on each patient's follow-up time and accrued expenses or encounter frequencies.

Statistical Analysis

Categorical variables are presented as frequencies (%) and compared using chi-square test. Continuous variables are presented as mean ± standard deviation and median (quantile 1, quantile 3). Fisher's exact tests and/or other non-parametric tests were applied as appropriate. Propensity-score matching was used to adjust for confounding using a greedy 1:1 matching algorithm. Propensity scores were calculated for each patient via a logistic regression model adjusting for baseline comorbidities, aggregated baseline charges and medical encounter visits, and several interval factors occurring after index hospital discharge and preceding treatment escalation. These interval factors included ACS events, revascularization, stroke, days until therapy switch, and aggregated interval charges and visit frequencies. Descriptive statistics for the pre-matched and propensity-matched cohort were summarized for all characteristics included within the propensity score model to evaluate balance between treatment groups. Charges and healthcare resource utilization were similarly examined. To assess the average effect of treatment escalation on outcomes, generalized linear models were fitted using a log-link function with gamma distribution or lognormal distribution, depending on the outcome of interest, to adjust for the correlation between the PS-matched groups. Modified park tests and distribution modeling were employed to confirm use of the most appropriate distribution. All statistical testes were two-tailed

with α=0.05 threshold for significance. All data and statistical processes were performed using SAS software (version 9.4; Cary, NC USA).

RESULTS

Study Population

There were 91,682 individuals admitted to the hospital with an acute coronary syndrome who underwent percutaneous coronary intervention. Only 71,287 (77%) had 6-months of insurance eligibility prior to index hospitalization. After applying the exclusion criteria, there were 21,103 (23%) initiated on clopidogrel, 5,040 (6%) initiated on prasugrel, and 2,974 (3%) initiated on ticagrelor lowing PCI. Of the clopidogrel initiators, 132 switched to ticagrelor and 281 switched to prasugrel (Figure 1).

Unmatched Characteristics and Outcomes

Prior to propensity-score matching, ticagrelor switchers had higher rates of hypertension, hyperlipidemia, chronic kidney disease, and congestive heart failure (Table 1). Ticagrelor switchers also had higher rates of ACE/ARB, beta-blocker, statin, and diabetic medication use. There was no difference between groups in charges associated with all-cause, cardiovascular, and bleeding-related expenditures (Table 2). Patients that switched to ticagrelor had similar cardiovascular-related prescription expenditures than prasugrel switchers ($360 ±417 vs. $410 ±864 PPPM, t-test p=0.52). There was no difference found between groups in HRU for all-cause, cardiovascular, or bleeding-related encounters.

Propensity-Score Model

Variable selected for baseline confounding adjustment were selected in accordance with clinical appropriateness and similar studies within this disease category. All variables were included in the propensity-score model. Of the 137 patients that switched to ticagrelor from clopidogrel and 281 that switched to prasugrel, 123 pairs were selected by the 1:1 greedy matching algorithm. Standardized differences after matching were below the 10% threshold, indicating that the cohorts were well balanced, except for percutaneous coronary intervention, ACE/ARB use, and interval PPPM costs (Table 1). There was no statistical difference between the frequency of baseline confounders after propensity-score matching. On average, ticagrelor escalators had less days of follow-up when compared to the prasugrel group (208 ±116 vs. 240 ±109 days, t-test p=0.03).

Healthcare Charges

After 1:1 PS-matching, average PPPM costs between groups were largely influenced by the highest cost patients as indicated by large standard deviations. The mean PPPM all-cause cost (ticagrelor vs. prasugrel: $12,137 ±37,016 vs. $18,233 ±71,336 PPPM) was largely driven by the cost associated with inpatient hospitalizations ($10,157 ±35,595 vs. $15,835 ±71,576 PPPM) (Table 2). This relationship remained consistent with mean cardiovascular-related total costs ($2,155 ±6,313 vs. $4,340 ±22,627 PPPM) being largely influenced by the cardiovascular inpatient costs ($1,647 ±6,321 vs. $3,720 ±22,633 PPPM). All-cause outpatient costs were lower among patients that escalated treatment to ticagrelor when compared to those escalating to prasugrel (Median

[Quantile 1; Quantile3]: $114 [0; 860] vs. $312 [0; 1,343], p=0.03). There were no significant differences in distributions between groups of other cost outcomes (Table 3).

Healthcare Resource Utilization

The mean PPPM HRU was similar among those who switched from clopidogrel to ticagrelor or to prasugrel for all-cause HRU (4.5 ±9.3 vs. 5.5 ±7.4 PPPM), outpatient (2.09 ±5.21 vs. 2.3 ±4.55 PPPM) and inpatient (2.45 ±6.90 vs. 2.23 ±6.91 PPPM) encounters (Table 2). Ticagrelor escalators had significantly lower PPPM all-cause outpatient HRU when compared to prasugrel escalators (0.6 [0; 3.1] vs. 1.0 [0; 2.9] PPPM, Wilcoxon sign-rank test p=0.03) (Table 3). However, there was no difference in all-cause total healthcare encounters [2.6 [1.1; 4.4] vs. 2.9 [1.5; 6.4] PPPM, p=0.08) or all-cause inpatient hospitalizations (0 [0; 3.1] vs. 0 [0; 2.9], p=0.91).

Measures of Treatment Effect from Generalized Linear Models

Generalized linear models were implemented to evaluate the rate ratio (RR) and 95% confidence interval (95%CI) among each outcome within the matched pairs (Table 4). The cost outcomes were modeled with a gamma distribution and the HRU outcomes were modeled using a lognormal distribution to appropriately accommodate the skewness of the observed datapoints. Patients who escalated to ticagrelor experienced 33% lower all-cause costs (RR: 0.67, 95%CI: 0.44-0.99, p=0.05) when compared to those switching to prasugrel. There was no significant difference found in all-cause outpatient (RR: 0.94, 95%CI: 0.60-1.48, p=0.80), hospitalizations (RR: 0.58, 95%CI: 0.31-1.07, p=0.08), or prescription (RR: 0.82, 95%CI: 0.64-1.05, p=0.12) costs. The

ticagrelor escalators also experienced 49% lower CV-related total costs (RR: 0.51, 95%CI: 0.33-0.76, p<0.01) driven by the 61% lower CV inpatient costs (RR: 0.39, 95%CI: 0.16-0.96, p=0.04). There was no difference in outpatient costs between groups (RR: 1.55, 95%CI: 0.72-3.3,3 p=0.27).

There was no difference found between groups for all-cause HRU (RR:0.82, 95%CI: 0.54-1.25, p=0.36), outpatient encounters (RR: 0.76, 95%CI: 0.41-1.42, p=0.39), or inpatient hospitalizations (RR: 0.91, 95%CI: 0.52-1.59, p=0.74). Similarly, there was no difference found in CV-related HRU (RR:0.77, 95%CI: 0.65-1.07, p=0.45), CV outpatient encounters (RR: 1.27, 95%CI: 0.49-3.32, p=0.62), or CV hospitalizations (RR: 0.55, 95%CI: 0.19-1.61, p=0.27).

DISCUSSION

This study found that there were favorable differences in total all-cause costs, total cardiovascular-related costs, and cardiovascular-related hospitalization costs among patients escalating antiplatelet therapy from clopidogrel to ticagrelor. While direct comparisons of the PPPM costs and HRU among propensity matched pairs derived non-significant findings, we postulate that the combination of small sample size and extreme values were the primary factors deriving this result as average values were consistently lower among ticagrelor switchers. The wide range in values were driven by extended inpatient hospitalizations where patients accrued many thousands of dollars of expenditures per day. Even though the data points for these costs are distributional outliers, these cases are clinically relevant and were kept in the sample. The top ten most

costly patients had extended hospitalizations related to myocardial infarction with secondary diagnosis codes for respiratory arrest, congestive heart failure, palliative care, end stage renal disease, and post-operative infections and were disproportionally attributed to prasugrel over ticagrelor escalators.

While we found that escalating to ticagrelor did not influence HRU, it was associated with lower all-cause medical costs and cardiovascular hospitalization costs. These findings indicate that patients who escalate to ticagrelor experienced less complicated and costly cardiovascular hospitalizations that those that switched to prasugrel. As such, escalating to ticagrelor should be considered, especially, if health system cost is the primary consideration.

To our knowledge there are no other studies investigating costs and healthcare resource utilization in patients escalating dual antiplatelet therapy from clopidogrel to either ticagrelor or prasugrel. It is difficult to compare the results from this study to others as the patients that escalate treatment are, likely, those who fail or are intolerant to clopidogrel. It is plausible that the similarities in mechanism of action of clopidogrel and prasugrel could contribute to lower costs in the ticagrelor escalators if clopidogrel-resistant patients experience some level of residual resistance to prasugrel and subsequently more costly outcomes. There have been many pharmacodynamic studies concluding that the degree of P2Y12 receptor inhibition is similar when comparing platelet reactivity following treatment escalation with prasugrel or ticagrelor.[6] However,

the translation of acceptable platelet reactivity to longitudinal cost and healthcare resource utilization has not been evaluated.

LIMITATIONS

Our study was subjected to limitations that could implicate some level of residual confounding. After the inclusion and exclusion criteria were applied to the data, a small population of patients that escalated to either ticagrelor or prasugrel remained. After 1:1 matching only 123 patient-pairs were included in the analyses. This sample size, coupled with extreme outcome values attributed to high-cost and healthcare ultra-utilizers, made it difficult to identify statistically significant differences of lower magnitudes – even though several hundreds of dollars difference may be meaningful. Additionally, over-the-counter medications were not captured within this dataset. Aspirin, an over-the-counter medication, is a fundamental aspect of dual-antiplatelet therapy and its utilization could not be evaluated. As such, we assumed that aspirin utilization was not different between groups. Third, this study utilized insurance claims data and was exposed to the limitations associated with retrospective studies of this type. Additional limitations regarding this data set include generalizability to low income or age 65+ individuals as only a portion of these patients are included within this database. Fourth, the 1:1 PS-greedy matching approach created comparable comparator groups. However, we excluded 14 (10%) unmatched patients who switched to ticagrelor. This potentially lowers the statistical power and makes our results more conservative.

CONCLUSION

We found that patients escalating antiplatelet therapy from clopidogrel to ticagrelor were associated with less total all-cause costs and total cardiovascular-related costs driven by lower cardiovascular-related hospitalization costs when compared to patients escalating to prasugrel. Future research with larger sample size is needed to fully evaluate differences in healthcare resource utilization between these drug regimens.

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Figure 1. Study population

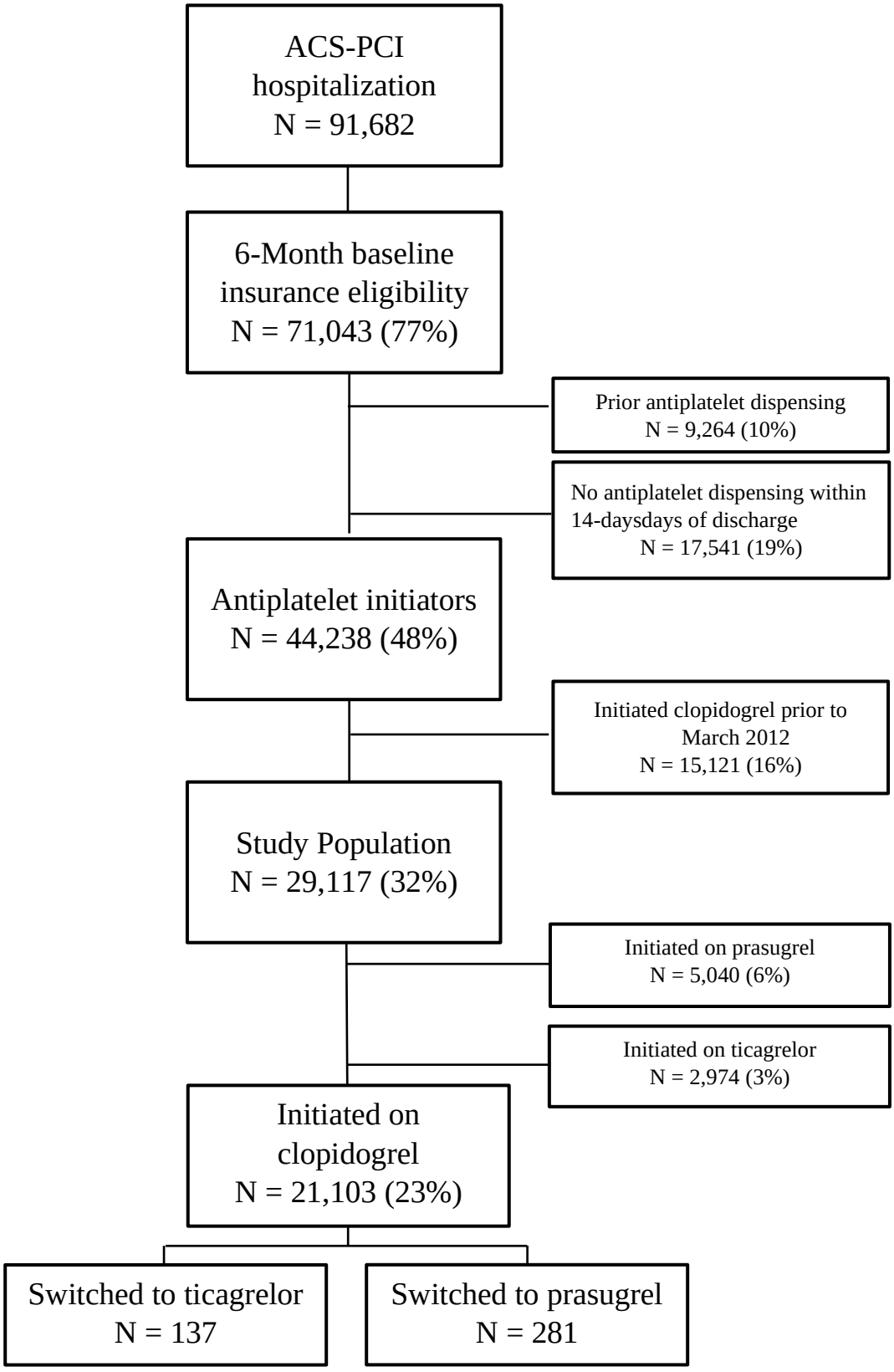


Table 1. Baseline and interval comorbidities for unmatched and 1:1 PS-matched cohorts with standardized differences (Std-diff)

	Unmatched Cohort			1:1 Matched Cohort			
Characteristics	Ticagrelor n = 137	Prasugrel n = 281	p*	Ticagrelor n = 123	Prasugrel n = 123	p*	Std-diff
Baseline							
Age (Mean ±SD)	63.7 ±12.5	61.9 ±11	0.15	63.3 ±12.4	62.4 ±11.1	0.23	0.08
Female	43 (31)	98 (35)	0.48	42 (34)	40 (33)	0.79	0.03
Insurance Type							
Commercial	72 (53)	171 (61)	0.12	71 (58)	76 (62)	0.52	0.05
Medicare	63 (46)	108 (38)		52 (42)	47 (38)		
Tobacco	26 (19)	81 (29)	0.03	25 (20)	20 (16)	0.41	0.02
Hypertension	112 (82)	218 (78)	0.33	98 (80)	104 (85)	0.32	0.10
Hyperlipidemia	113 (82)	213 (76)	0.12	101 (82)	101 (82)	0.99	0.02
Carotid Artery Stenosis	9 (7)	19 (7)	0.94	6 (5)	7 (6)	0.78	0.03
Chronic Kidney Disease	16 (12)	16 (6)	0.03	10 (8)	12 (10)	0.66	0.03
Anemia	17 (12)	25 (9)	0.26	12 (10)	12 (10)	0.99	<0.01
Chronic Obstructive Pulmonary Disease	20 (15)	52 (19)	0.32	18 (15)	17 (14)	0.86	0.02
Asthma	11 (8)	17 (6)	0.45	10 (8)	7 (6)	0.45	0.06
Percutaneous Coronary Intervention	49 (36)	65 (23)	<0.01	39 (32)	31 (25)	0.26	0.14
Percutaneous Coronary Angioplasty	15 (11)	27 (10)	0.67	11 (9)	15 (12)	0.41	<0.01
Coronary Artery Bypass	11 (8)	19 (7)	0.64	9 (7)	9 (7)	0.99	<0.01
Congestive Heart Failure	38 (28)	56 (20)	0.07	28 (23)	33 (27)	0.46	0.04
Atrial Fibrillation	18 (13)	32 (11)	0.61	14 (11)	20 (16)	0.27	<0.01
Medications							

ACE/ARB	61	(45)	101	(36)	0.09	53	(43)	54	(44)	0.90	0.11
Beta-Blocker	51	(37)	77	(27)	0.04	42	(34)	44	(36)	0.79	0.03
Diuretic	27	(20)	73	(26)	0.56	18	(15)	24	(20)	0.31	0.04
Statin	68	(50)	99	(35)	<0.01	58	(47)	58	(47)	0.99	<0.01
Diabetes	43	(31)	65	(23)	0.07	35	(28)	33	(27)	0.78	0.05
Proton-Pump Inhibitor	35	(26)	64	(23)	0.53	30	(24)	29	(24)	0.88	0.04
Anticoagulant	5	(4)	10	(4)	0.95	5	(4)	4	(3)	0.73	0.04
Clopidogrel	19	(14)	20	(7)	0.02	13	(11)	12	(10)	0.83	0.03
Strong CYP P-450 Inducers/Inhibitors	14	(10)	29	(10)	0.99	13	(11)	17	(14)	0.44	0.10
Baseline PPPM Costs (Mean ±SD)	24,715	±4,979	14,316	±31,525	0.01	16,600	±34,034	17,765	±35,331	0.79	0.03
Baseline PPPM HRU (Mean ±SD)	3.9	±6.73	2.5	±2.93	<0.01	2.9	±3.2	2.9	±3.5	0.94	0.01
Pre-Switch (Interval)											
Myocardial Infarction	10	(7)	14	(5)	0.33	7	(6)	6	(5)	0.78	0.04
Stroke	0	(0)	0	(0)	-	0	(0)	0	(0)	-	-
Percutaneous Coronary Intervention	27	(20)	24	(9)	<0.01	19	(15)	17	(14)	0.72	0.05
Days until Switch											
Early: 1-30 days	42	(31)	118	(42)	0.03	40	(33)	51	(41)	0.14	0.04
Late: 30-365 days	93	(68)	161	(57)		89	(72)	72	(59)		
Interval PPPM Costs (Mean ±SD)	34,843	±56,378	53,319	±128,843	0.12	36,386	±58,646	42,396	±52,122	0.41	0.11
Interval PPPM HRU (Mean ±SD)	4.4	±6.9	4.8	±4.2	0.46	4.3	±5.8	4.6	±4.9	0.74	0.04

*The p-values presented were calculated using t-test and X^2-test for unmatched and student t-test and McNemar's test for matched pairs.

Table 2. Average per-patient per-month charges and healthcare resource utilization for unmatched and propensity-score matched patients during follow-up period

	Unmatched Cohort				**1:1 Matched Cohort**			
Outcomes (PPPM Mean ±SD)	Ticagrelor n = 137		Prasugrel n = 281		Ticagrelor n = 123		Prasugrel n = 123	
All-Cause								
Total Cost ($)	26,124	±99,995	13,281	±5,541	12,137	±37,016	18,233	±71,336
Outpatient Cost ($)	1,474	±5,070	2,445	±6,633	1,618	±5,291	1,937	±4,261
Inpatient Cost ($)	24,290	±99,748	10,425	±55,564	10,157	±35,595	15,835	±71,576
Rx Cost ($)	360	±418	411	±867	362	±422	460	±1,193
Number of Encounters	6.7	±13.7	5.7	±11.7	4.5	±9.3	5.5	±7.4
Outpatient Encounter	1.9	±5.0	2.9	±8.3	2.1	±5.2	2.3	±4.6
Hospitalizations	4.8	±12.8	2.8	±8.5	2.5	±6.9	3.2	±7.0
Cardiovascular								
Total Cost ($)	3,473	±13,779	2,639	±15,441	2,155	±6,313	4,340	±22,627
Outpatient Cost ($)	136	±744	308	±1,596	146	±769	184	±667
Inpatient Cost ($)	2,976	±13,827	1,920	±15,382	1,647	±6,321	3,720	±22,633
Rx Cost ($)	360	±417	410	±864	363	±420	435	±1,150
Number of Encounters	0.5	±1.3	0.4	±1.1	0.4	±1.0	0.5	±1.2
Outpatient Encounter	0.2	±0.8	0.2	±0.7	0.2	±0.8	0.1	±0.3
Hospitalizations	0.3	±1.1	0.2	±0.9	0.2	±0.7	0.3	±1.2

Table 3. Distributional characteristics of per-patient per-month charges and healthcare resource utilization for unmatched and propensity-score matched patients during follow-up period

	Unmatched Cohort						
Outcomes	Ticagrelor n = 137			Prasugrel n = 281			**p***
All-Cause	Median	Quantile 1	Quantile 3	Median	Quantile 1	Quantile 3	
Total Cost ($)	2,044	765	10,469	2,090	942	7,124	0.62
Outpatient Cost ($)	26	0	670	510	0	1,820	0.01
Inpatient Cost ($)	0	0	8,591	0	0	1,745	0.11
Rx Cost ($)	270	13	515	251	94	462	0.21
Number of Encounters	2.9	1.1	5.6	2.9	1.4	5.6	0.05
Outpatient Encounter	0.3	0.0	1.9	1.4	0.0	3.4	0.19
Hospitalizations	0.0	0.0	3.4	0.0	0.0	1.9	0.02
Cardiovascular							
Total Cost ($)	456	213	1,025	403	205	851	0.14
Outpatient Cost ($)	0	0	0	0	0	33	<0.01
Inpatient Cost ($)	0	0	33	0	0	0	0.01
Rx Cost ($)	270	73	515	255	98	458	0.42
Number of Encounters	0.0	0.0	0.4	0.0	0.8	0.3	0.19
Outpatient Encounter	0.0	0.0	0.0	0.0	0.0	0.1	<0.01
Hospitalizations	0.0	0.0	0.9	0.0	0.0	0.0	0.05

Table 3. Continued

Outcomes	1:1 Matched Cohort						
	Ticagrelor n = 123			Prasugrel n = 123			p*
All-Cause	Median	Quantile 1	Quantile 3	Median	Quantile 1	Quantile 3	
Total Cost ($)	1,795	699	8,145	2,132	876	8,865	0.75
Outpatient Cost ($)	114	0	860	312	0	1,343	0.03
Inpatient Cost ($)	0	0	3,324	0	0	3,508	0.21
Rx Cost ($)	265	105	458	272	81	426	0.40
Number of Encounters	2.6	1.1	4.4	2.9	1.5	6.4	0.08
Outpatient Encounter	0.6	0.0	2.1	1.0	0.0	2.9	0.03
Hospitalizations	0.0	0.0	3.1	0.0	0.0	2.9	0.91
Cardiovascular							
Total Cost ($)	408	181	949	433	196	865	0.86
Outpatient Cost ($)	0	0	0	0	0	23	0.32
Inpatient Cost ($)	0	0	7	0	0	0	0.74
Rx Cost ($)	271	80	429	246	72	460	0.84
Number of Encounters	0.0	0.0	0.3	0.1	0.0	0.5	0.18
Outpatient Encounter	0.0	0.0	0.0	0.0	0.0	0.1	0.40
Hospitalizations	0.0	0.0	0.0	0.0	0.0	0.0	0.32

*The p-values presented were calculated using Mann-Whitney U-test for unmatched and Wilcoxon signed-rank test for matched cohorts

Table 4. Adjusted Results of Generalized Linear Model

Outcomes*	Rate Ratio	95% Confidence Interval		p	Distribution
All-Cause					
Total Cost ($)	**0.67**	**0.44**	**0.99**	**0.05**	Gamma
Outpatient Cost ($)	0.94	0.60	1.48	0.80	Gamma
Inpatient Cost ($)	0.58	0.31	1.07	0.08	Gamma
Rx Cost ($)	0.82	0.64	1.05	0.12	Gamma
Number of Encounters	0.82	0.54	1.25	0.36	LogNormal
Outpatient Encounter	0.76	0.41	1.42	0.39	LogNormal
Hospitalizations	0.91	0.52	1.59	0.74	LogNormal
Cardiovascular					
Total Cost ($)	**0.51**	**0.33**	**0.76**	**<0.01**	Gamma
Outpatient Cost ($)	1.55	0.72	3.33	0.27	Gamma
Inpatient Cost ($)	**0.39**	**0.16**	**0.96**	**0.04**	Gamma
Rx Cost ($)	0.83	0.65	1.07	0.15	Gamma
Number of Encounters	0.77	0.39	1.52	0.45	LogNormal
Outpatient Encounter	1.27	0.49	3.32	0.62	LogNormal
Hospitalizations	0.55	0.19	1.61	0.27	LogNormal

* For all models, results are presented for ticagrelor = 1

Table 5. Distributional statistics for all-cause outcomes

	Unmatched			1:1 PS-Matched		
PPPM Total Cost	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	135	279		123	123	
Max ($)	1,033,226	635,608		294,777	635,607	
Q3 ($)	10,469	7,124		8,145	8,865	
Median ($)	2,044	2,090	0.92*	1,795	2,132	0.37*
Q1 ($)	765	942		699	876	
Min ($)	6	28		6	40	
Mean ($)	26,124	13,281	0.09**	12,137	18,233	0.40**
Standard Deviation ($)	99,995	5,541		37,016	71,336	

	Unmatched			1:1 PS-Matched		
PPPM Outpatient Costs	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	135	279		123	123	
Max ($)	45,811	81,469		45,810	25,465	
Q3 ($)	670	1,820		860	1,343	
Median ($)	26	510	<0.01	114	312	0.06*
Q1 ($)	0	0		0	0	
Min ($)	0	0		0	0	
Mean ($)	1,474	2,445	0.13**	1,618	1,937	0.60**
Standard Deviation ($)	5,070	6,633		5,291	4,261	

	Unmatched			1:1 PS-Matched		
PPPM Inpatient Cost	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	135	279		123	123	
Max ($)	1,033,226	635,146		294,634	635,145	
Q3 ($)	8,591	1,745		3,324	3,508	
Median ($)	0	0	<0.01	0	0	0.51*
Q1 ($)	0	0		0	0	
Min ($)	0	0		0	0	

Mean ($)	24,290	10,425	0.07**	10,157	15,835	0.43**
Standard Deviation ($)	99,748	55,564		35,595	71,576	

	Unmatched			1:1 PS-Matched		
PPPM Prescription Cost	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	135	279		123	123	
Max ($)	2,365	12,585		12,585	2,365	
Q3 ($)	515	462		458	426	
Median ($)	270	251	0.60*	265	272	0.70*
Q1 ($)	73	94		105	81	
Min ($)	0	0		0	0	
Mean ($)	360	411	0.51**	362	460	0.01**
Standard Deviation ($)	418	867		422	1,193	

	Unmatched			1:1 PS-Matched		
PPPM No. of Encounters	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	135	279		123	123	
Max	98.2	137		83.7	43.7	
Q3	5.58	5.57		4.42	6.35	
Median	2.90	2.88	0.92*	2.57	2.88	0.52*
Q1	1.09	1.43		1.06	1.45	
Min	0.00	0.00		0.00	0.09	
Mean	6.66	5.67	0.03**	4.54	5.53	0.35**
Standard Deviation	13.74	11.67		9.25	7.43	

	Unmatched			1:1 PS-Matched		
PPPM No. Outpatient Encounters	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	135	279		123	123	
Max	49.0	126		49.0	43.4	
Q3	1.94	3.36		2.14	2.94	

Median	0.25	1.37	<0.01	0.62	1.01	0.16*
Q1	0.00	0.00		0.00	0.00	
Min	0.00	0.00		0.00	0.00	
Mean	1.91	2.90	0.21**	2.09	2.30	0.37**
Standard Deviation	5.01	8.35		5.21	4.55	

	Unmatched			**1:1 PS-Matched**		
PPPM No. Hospitalizations	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	135	279		123	123	
Max	98.2	95.5		63.5	38.3	
Q3	3.40	1.90		3.07	2.88	
Median	0.00	0.00	<0.01	0.00	0.00	0.60*
Q1	0.00	0.00		0.00	0.00	
Min	0.00	0.00		0.00	0.00	
Mean	4.75	2.77	0.06**	2.45	3.23	0.74**
Standard Deviation	12.76	8.51		6.90	6.97	

*The p-value presented was calculated to compare distributions Mann-Whiney U for unmatched and Wilcoxon singed-rank test for matched pairs

**The p-value presented was calculated to compare the distributional mean using a t-test for unmatched and student t-test for matched pairs

Table 6. Distributional statistics for cardiovascular outcomes

	Unmatched			1:1 PS-Matched		
PPPM Total CV Cost	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	137	281		128	128	
Max ($)	144,736	226,693		43,685	226,693	
Q3 ($)	1,025	851		949	865	
Median ($)	456	403	0.60*	408	433	0.80*
Q1 ($)	213	205		181	196	
Min ($)	0	0		0	0	
Mean ($)	3,473	2,639	0.13**	2,155	4,340	0.29**
Standard Deviation ($)	13,779	15,441		6,313	22,627	

	Unmatched			1:1 PS-Matched		
PPPM Outpatient CV Costs	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	137	281		128	128	
Max ($)	7,380	20,138		7,380	4,986	
Q3 ($)	0	33		0	23	
Median ($)	0	0	<0.01*	0	0	<0.01*
Q1 ($)	0	0		0	0	
Min ($)	0	0		0	0	
Mean ($)	136	308	0.23**	146	184	0.67**
Standard Deviation ($)	744	1,596		769	667	

	Unmatched			1:1 PS-Matched		
PPPM Inpatient CV Cost	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	137	281		128	128	
Max ($)	144,736	226,231		43,402	226,231	
Q3 ($)	33	0		7	0	

Median ($)	0	0	0.03*	0	0	0.56*
Q1 ($)	0	0		0	0	
Min ($)	0	0		0	0	
Mean ($)	2,976	1,920	0.16**	1,647	3,720	0.31**
Standard Deviation ($)	13,827	15,382		6,321	22,633	

	Unmatched			1:1 PS-Matched		
PPPM CV Prescription Cost	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	137	281		128	128	
Max ($)	2,365	12,585		2,365	12,585	
Q3 ($)	515	458		429	460	
Median ($)	270	255	0.75*	271	246	0.45*
Q1 ($)	73	98		80	72	
Min ($)	0	0		0	0	
Mean ($)	360	410	0.52**	363	435	0.50**
Standard Deviation ($)	417	864		420	1,150	

	Unmatched			1:1 PS-Matched		
PPPM No. of CV Encounters	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	137	281		128	128	
Max	10.00	10.89		8.14	10.89	
Q3	0.35	0.34		0.34	0.51	
Median	0.00	0.08	0.10*	0.00	0.10	0.02*
Q1	0.00	0.00		0.00	0.00	
Min	0.00	0.00		0.00	0.00	
Mean	0.47	0.38	0.45**	0.36	0.47	0.44**
Standard Deviation	1.34	1.07		1.03	1.21	

	Unmatched			1:1 PS-Matched		
PPPM No. Outpatient CV Encounters	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	137	281		128	128	
Max	8.14	10.00		8.14	2.11	
Q3	0.00	0.13		0.00	0.13	
Median	0.00	0.00	<0.01*	0.00	0.00	<0.01*
Q1	0.00	0.00		0.00	0.00	
Min	0.00	0.00		0.00	0.00	
Mean	0.17	0.17	0.96**	0.18	0.14	0.61**
Standard Deviation	0.79	0.66		0.81	0.34	

	Unmatched			1:1 PS-Matched		
PPPM No. Inpatient CV Encounters	Ticagrelor	Prasugrel	p	Ticagrelor	Prasugrel	p
N	137	281		128	128	
Max	10.00	10.89		6.74	10.89	
Q3	0.09	0.00		0.00	0.00	
Median	0.00	0.00	0.08*	0.00	0.00	0.88*
Q1	0.00	0.00		0.00	0.00	
Min	0.00	0.00		0.00	0.00	
Mean	0.30	0.22	0.38**	0.18	0.32	0.23**
Standard Deviation	1.12	0.88		0.68	1.20	

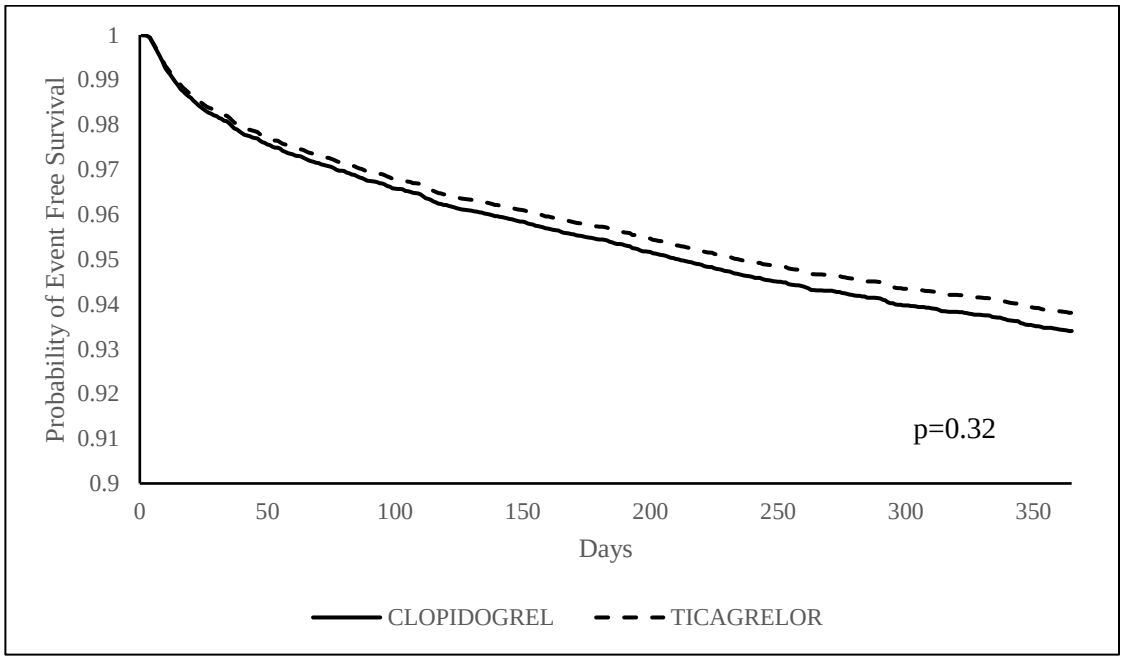
*The p-value presented was calculated to compare distributions Mann-Whiney U for unmatched and Wilcoxon singed-rank test for matched pairs

**The p-value presented was calculated to compare the distributional mean using a t-test for unmatched and student t-test for matched pairs

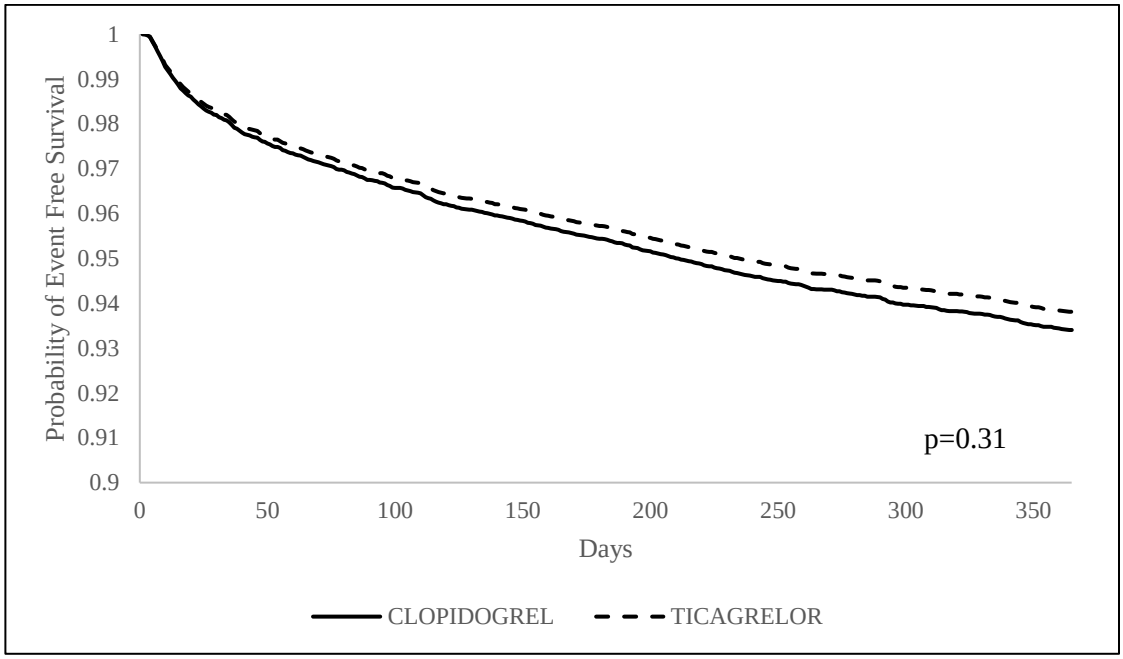
APPENDIX A

A.1-A.5 SUPPLIMENTAL FIGURES FOR MANUSCRIPT 1:

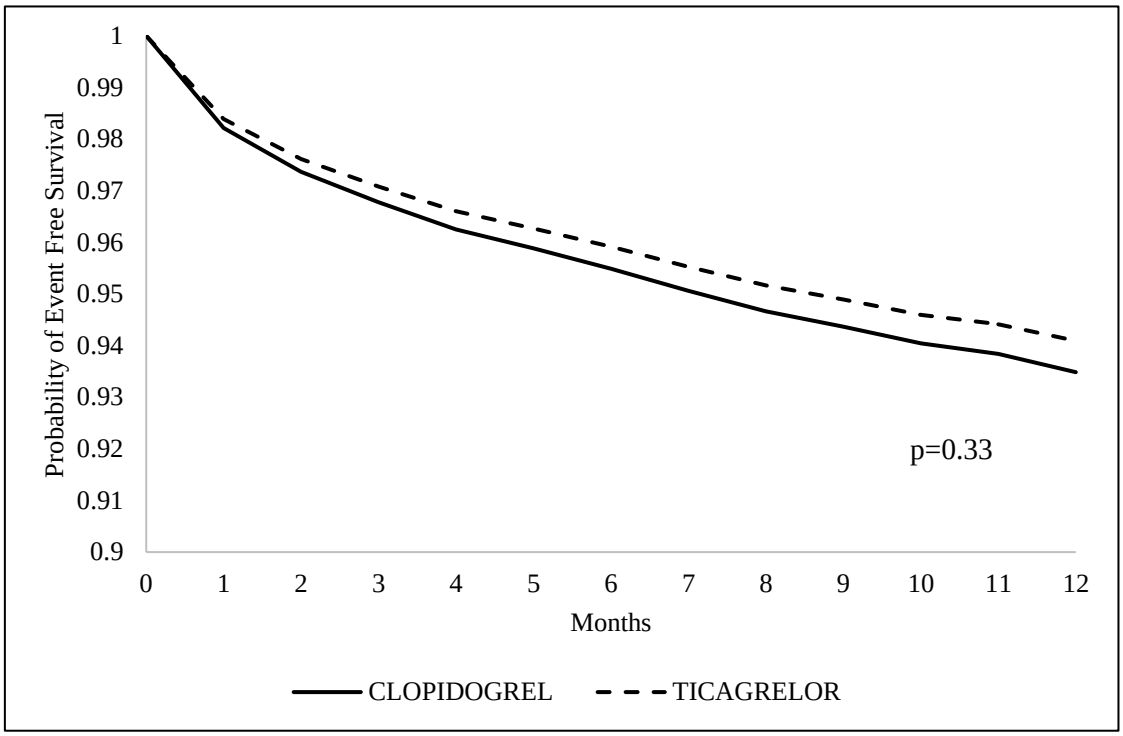
Appendix Figure A.1: Intention-to-treat (ITT) estimated probability of event-free survival for death, myocardial infarction, or stroke in clopidogrel versus ticagrelor following an acute coronary syndrome



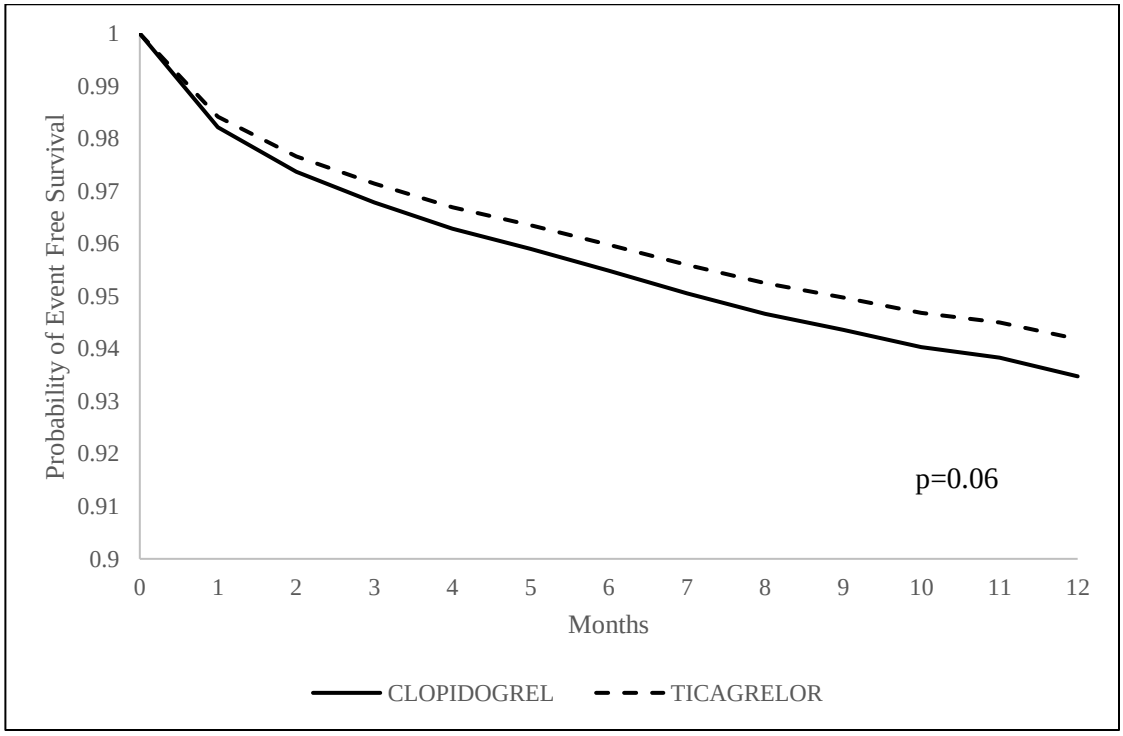
Appendix Figure A.2: As-treated (AT) estimated probability of event-free survival for death, myocardial infarction, or stroke in clopidogrel versus ticagrelor following an acute coronary syndrome



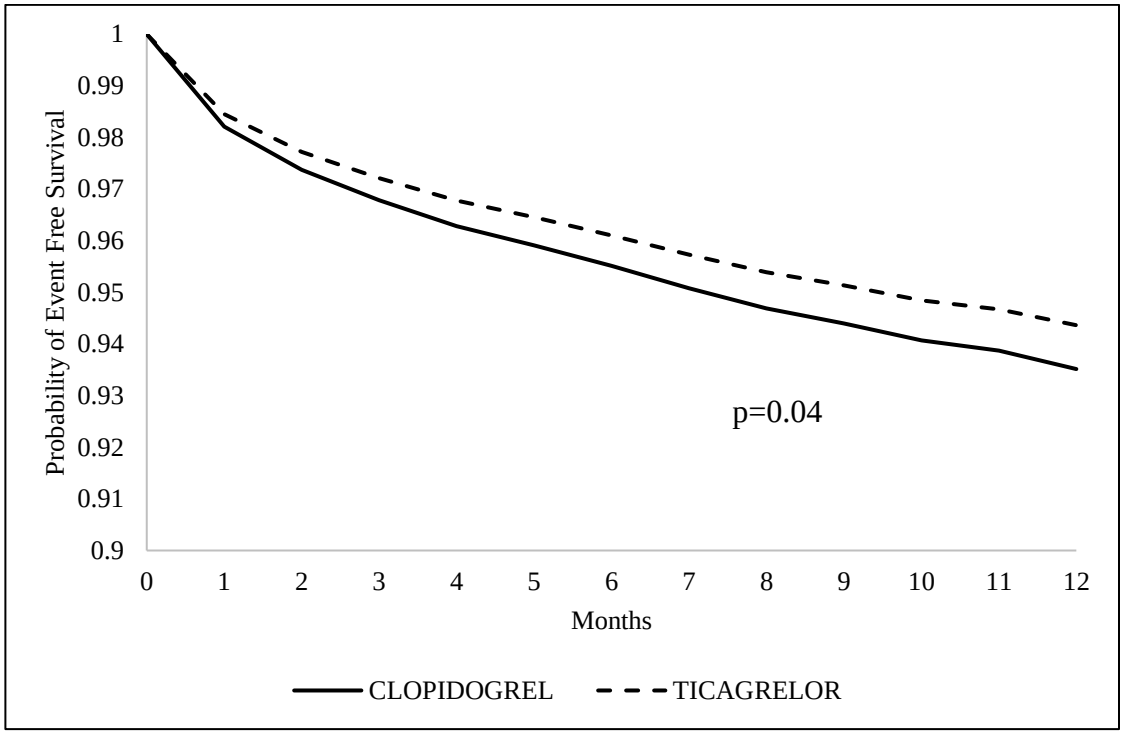
Appendix Figure A.3: Intention-to-treat with censor-weighting (ITT-CW) estimated probability of event-free survival for death, myocardial infarction, or stroke in clopidogrel versus ticagrelor following an acute coronary syndrome



Appendix Figure A.4: Time-dependent exposure (TD) estimated probability of event-free survival for death, myocardial infarction, or stroke in clopidogrel versus ticagrelor following an acute coronary syndrome



Appendix Figure A.5: Time-dependent with censor-weighting (TD-CW) estimated probability of event-free survival for death, myocardial infarction, or stroke in clopidogrel versus ticagrelor following an acute coronary syndrome



APPENDIX B

Appendix Table B.1: Administrative claims codes for various comorbidities

Variable	Code	Code Type
Acute coronary syndromes	"410" "411"	ICD-9 Dx
Percutaneous coronary intervention	"3601" "3602" "3605" "3606" "3607" "3609" "0066" "92980" "92981" "92982" "92984"	CPT & IDC-9 Proc
Fibrinolysis	37201 "37211" "37212" "37213" "37214" "37195" "92977" "9910"	CPT & IDC-9 Proc
Tobacco	"3051" "V1582"	ICD-9 Dx
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"	ICD-9 Dx
Hyperlipidemia	"2720" "2721" "2722" "2723" "2724"	ICD-9 Dx

Diabetes mellitus	"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"	ICD-9 Dx
Coronary artery stenosis	"43310" "43311"	ICD-9 Dx
Peripheral vascular disease	"4400" "4401" "4402" "44020" "44021" "44022" "44023" "44029" "4404" "4408" "4409" "4439" "5570" "5571" "5579"	ICD-9 Dx
Dialysis	"5856"	ICD-9 Dx
Chronic Kidney Disease	"585" "5851" "5852" "5853" "5854" "5855" "5859"	ICD-9 Dx
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"	ICD-9 Dx

	"28481" "28489" "2849" "2850" "28521" "28522" "28529" "2858" "2859"	
Chronic obstructive pulmonary disorder	"490" "4910" "4911" "4912" "49120" "49121" "49122" "4918" "4919" "4920" "4928" "494" "4940" "4941" "496"	ICD-9 Dx
Asthma	"49300" "49301" "49302" "49310" "49311" "49312" "49320" "49321" "49322" "49381" "49382" "49390" "49391" "49392")	ICD-9 Dx
Congestive heart failure	"428" "4280" "4281" "4282" "42820" "42821" "42822" "42823" "4283" "42830" "42831" "42832" "42833" "4284" "42840" "42841" "42842" "42843" "4289"	ICD-9 Dx
Atrial fibrillation	"42731"	ICD-9 Dx

Appendix Table B.2: Coding algorithms for outcomes

ICD-9 Coding Algorithm		Exclusion	PPV	Source
Myocardial infarction[58]	3 <= LOS <= 180			
	410.xx	410.x2	0.94	Kiyota et al.
Ischemic stroke	3 <= LOS <= 180			
	433.x1		0.955	Wahl et al.
	434.x1			
Death				
	Optum Death File			
Intracranial hemorrhage	Any Position			
	430 (SAH)	800-804	0.86	Tirschwell et al.
	431 (ICH)	850-854	0.90	Tirschwell et al.
		V57		
Major GI Bleed	Any Position			
	531.0X		0.878	Wahl et al.
	531.2X			
	531.4X			
	531.6X			
	532.0X			
	532.2X			
	532.4X			
	532.6X			
	533.0X			
	533.2X			
	533.4X			
	533.6X			
	534.0X			
	534.2X			
	534.4X			
	534.6X			

	578.0			
	4443 (ICD-9 PROC)			
	43255 (CPT)			

APPENDIX C

Appendix Table C.1 Generic name roots for cardiovascular medications queried in Manuscript 3 for cardiovascular-related prescription costs

Generic Name Root			
BENAZEPRIL	FONDAPARINUX	NADOLOL	TRIAMTERENE
CAPTOPRIL	HEPARIN	NEBIVOLOL	EPLERENONE
ENALAPRIL	WARFARIN	PINDOLOL	SPIRONOLACTONE
LISINOPRIL	ASPIRIN	PROPANOLOL	AMILORIDE
QUINAPRIL	CILOSTAZOL	SOTALOL	TORSEMIDE
RAMIPRIL	CLOPIDOGREL	TIMOLOL	TRIAMTERENE
CANDESARTAN	DIPYRAMIDAMOLE	AMLODIPINE	ATORVASTATIN
EPROSARTAN	PRASUGREL	BEPRIDIL	FLUVASTATIN
IRBESARTAN	TICLOPIDINE	DILTIAZEM	LOVASTATIN
LOSARTAN	CLONIDINE	FELODIPINE	PRAVASTATIN
TELMISARTAN	DOXAZOSIN	ISRADIPINE	ROSUVASTATIN
VALSARTAN	HYDRALAZINE	NICARDIPINE	SIMVASTATIN
AMIODARONE	METHYLDOPA	NIFEDIPINE	FENOFIBRATE
DISOPYRAMIDE	MINOXIDIL	NISOLDIPINE	GEMFIBROZIL
DOFETILIDE	PHENOXYBENZAMINE	VERAPAMIL	COLESEVELAM
FLECAINIDE	PHENTOLAMINE	DIGOXIN	CHOLESTYRAMINE
MEXILETINE	PRAZOSIN	AMILORIDE	COLESTIPOL
PROCAINAMIDE	TERAZOSIN	BUMETANIDE	NIACIN
PROPAFENONE	ACEBUTOLOL	CHLOROTHIAZIDE	NITROGLYCERIN
QUINADINE	BETAXOLOL	ETHACRYNIC	RANOLAZINE
SOTALOL	BISOPROLOL	FUROSEMIDE	TICAGRELOR
TOCAINIDE	CARVEDILOL	HYDROCHLOROTHIAZIDE	
DALTEPARIN	LABETALOL	INDAPAMIDE	
ENOXAPARIN	METOPROLOL	METOLAZAONE	

Cytochrome_P450_3A4_and_3A5_Known_Drug_Interaction_Chart.pdf. https://www.mayocliniclabs.com/it-mmfiles/Cytochrome_P450_3A4_and_3A5_Known_Drug_Interaction_Chart.pdf. Accessed April 28, 2020.