The comparative effectiveness, safety, value, and adherence of newer P2Y12 inhibitors versus clopidogrel in the context of heterogeneity

Kangho Suh

A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2019

Reading Committee:

Anirban Basu, Chair

Joshua Carlson

Kelley Branch

Program Authorized to Offer Degree:

School of Pharmacy

University of Washington

Abstract

The comparative effectiveness, safety, value, and adherence of newer P2Y12 inhibitors versus clopidogrel in the context of heterogeneity

Kangho Suh

Chair of the Supervisory Committee:

Anirban Basu

Department of Pharmacy

Background

$P2Y_{12}$ inhibitors are a class of medications indicated with aspirin as part of dual antiplatelet therapy (DAPT) for patients with acute coronary syndrome after undergoing percutaneous coronary intervention (PCI). Taking a $P2Y_{12}$ inhibitor along with aspirin after PCI reduces the incidence of cardiovascular death, nonfatal MI, and stroke in the following year. Clopidogrel, the first oral $P2Y_{12}$ inhibitor, was approved in 1997 and was used widely as part of DAPT therapy. However, there are some issues with clopidogrel such as low bioavailability and slow onset of platelet inhibition compared to newer agents, heterogeneity in patient response, and drug resistance. These concerns were addressed with two newer oral agents, prasugrel and ticagrelor, which were approved in 2009 and 2011, respectively. This study aims to examine the heterogeneity in treatment effects of these antiplatelet agents and assess how healthcare providers and patients change their behaviors as a result. In Aim 1, I examined whether

physicians identify heterogeneity of treatment effects (HTE) with $P2Y_{12}$ inhibitors and change their prescribing patterns as a result. This is extended into Aim 2, which explored whether physicians' adaptions in prescribing patterns was a cost effective strategy. Aim 3 assessed patients' adherence to $P2Y_{12}$ inhibitors and determined if any factors were associated with heterogenous impacts along the adherence distribution.

Methods

In Aim 1, an instrumental variable approach with person-centered treatment effects was used to assess patient-level comparative effectiveness and safety outcomes from January 2010 to December 2017. These outcomes were used to study whether physician adapted their prescribing patterns over the study period to match the most optimal $P2Y_{12}$ inhibitor with the patient.

In Aim 2, results from Aim 1 were extended to develop a hybrid lifetime Markov model to assess whether physicians' adaptive prescribing with $P2Y_{12}$ inhibitors was a cost effective strategy compared to universal treatment with clopidogrel or the newer $P2Y_{12}$ inhibitors. Inputs for the 1-year short term model were informed from Aim 1 results, while inputs for the lifetime model were informed from the literature.

In Aim 3, conditional and unconditional quantile regression models were used along with more traditional logistic regression models to examine medication adherence of the three $P2Y_{12}$ inhibitor, and to determine which covariates had heterogenous impacts along the adherence distribution. Patients who received drug eluting stents were measured for 185 days.

Results

In Aim 1, 52,823 patients were included for analysis. Patients on ticagrelor and prasugrel had a significantly lower probability of major adverse cardiovascular events [-3.97 percentage points (95% CI, -6.97 to -0.26)] and significantly lower probability of major bleeding events [-2.93 percentage points (95% CI, -4.83 to -0.70)] compared to patients on clopidogrel. Physicians were able to better align patients who would benefit on clopidogrel from 17.39% in 2010 to 26.40% by 2015, but patient outcomes were not significantly different than when everyone received ticagrelor or prasugrel.

In Aim 2, physicians' adaptive prescribing resulted in 11.63 life-years (LYs), 9.92 quality-adjusted life-years (QALYs), and $72,403 total costs; universal clopidogrel resulted in 11.59 LYs, 9.84 QALYs, and $72,670 total costs; and universal prasugrel or ticagrelor resulted in 11.67 LYs, 10.00 QALYs, and $73,325 total costs. Universal treatment with prasugrel or ticagrelor was a dominant strategy compared to universal treatment with clopidogrel and a cost-effective strategy compared to targeted prescribing with an incremental cost-effectiveness ratio of $11,144/QALY.

In Aim 3, adherence to $P2Y_{12}$ inhibitors were generally high (88.74%, 90.52%, 88.95%, and 89.60% for branded clopidogrel, generic clopidogrel, prasugrel, and ticagrelor, respectively). The unconditional quantile regression approach showed prasugrel and ticagrelor had significantly lower adherence compared to branded clopidogrel, especially around the 30^{th} percentile. Other factors that impacted adherence the most were having comorbid depression and living in the southern region.

Conclusions

The research from this dissertation provided a deeper understanding of $P2Y_{12}$ inhibitors and how heterogeneity of treatment effects impacted physician prescribing and in turn the cost-effectiveness of targeted prescribing with these antiplatelet agents. This research also revealed which factors impacted adherence the most along the entire adherence distribution so that future strategies to improve adherence could be better informed.

Table of Contents

List of Figures

List of Tables

ACKNOWLEDGEMENTS

Throughout my five years at the University of Washington, I received a great deal of support and assistance. I would like to thank my dissertation chair Anirban Basu and my committee members Josh Carlson and Kelley Branch for their mentorship, expertise, and guidance. I learned so much from them throughout the process and will be forever grateful.

I would also like to thank Ryan Hansen who served as my academic advisor during my first two years of the PhD program. He always gave me great advice and made sure I was managing a good work-life balance. Another faculty member who helped me think critically about research throughout my years was Aasthaa Bansal. I am grateful I was able to learn from her expertise as a biostatistician from my independent study.

The support of my fellow students, colleagues, and friends in the CHOICE Institute made the PhD process much easier to endure. Each student is amazing in his or her own way, and I look forward to collaborating on future projects with everyone. Finally, a special thank you to my family for encouraging me when times were tough and giving me the strength to cross the finish line.

Chapter 1: Addressing heterogeneity of treatment effects and targeted treatment of $P2Y_{12}$ inhibitors using a novel instrumental variable method

Abstract

Importance: Clopidogrel and newer $P2Y_{12}$ inhibitors are a mainstay of dual antiplatelet therapy after acute coronary syndrome patients undergo percutaneous coronary intervention. There is less understanding as to how patients were selected to receive the newer antiplatelets, and especially if better "passive" personalization of $P2Y_{12}$ inhibitors receipt was achieved over time, presumably through a learning-by-doing process.

Objective: To evaluate personalized prescribing behavior from physicians with $P2Y_{12}$ inhibitors, and its impact on patient outcomes.

Design, Setting, and Participants: This retrospective cohort study included 52,891 patients with acute coronary syndrome from IBM® MarketScan® Research Databases who had an incident percutaneous coronary intervention and an incident prescription fill for a $P2Y_{12}$ inhibitor from January 1, 2010 to December 31, 2016. A novel instrumental variable method assessed patient-level comparative effectiveness and safety outcomes through December 31, 2017. We examined changes in $P2Y_{12}$ physician prescribing patterns over the study period and classified personalization as when receipt of $P2Y_{12}$ inhibitors aligned with their predicted dominance over clopidogrel at the patient level.

Exposure(s): $P2Y_{12}$ inhibitors (prasugrel, ticagrelor) compared to clopidogrel prescriptions

Main Outcome(s) and Measure(s): The primary effectiveness outcome was major adverse cardiovascular events of myocardial infarction, death, in-hospital mortality, and revascularization and major bleeding.

Results: The estimated average risk difference favored ticagrelor or prasugrel over clopidogrel by improving the effectiveness outcome [-3.97 percentage points (95% CI, -6.97 to -0.26)] and the safety outcome [-2.93 percentage points (95% CI, -4.83 to -0.70)]. However, heterogeneity analysis suggests that 19.89% of patient would benefit from clopidogrel, either on the effectiveness or the safety side. In 2010, the clopidogrel personalization match quality was at 17.39%. Over time, this quality increased to 26.40% by 2015, to the extent that realized patient outcomes were not significantly different than when everyone had received newer $P2Y_{12}$ inhibitors. The predominant motivation behind improving match quality seem to be driven by clopidogrel's safety profile in select patients.

Conclusions and Relevance: Increased adoption of newer $P2Y_{12}$ inhibitors seems to be associated with improved health outcomes in patients due to improving "passive" personalization of these treatments. This suggests personalization can lead to significant cost-savings, although there remains significant room for improvement in match quality that could further reduce risks in major adverse cardiovascular events and major bleeding.

Background

$P2Y_{12}$ inhibitors with aspirin as dual antiplatelet therapy (DAPT)[1-3] are guideline-based therapy for patients with acute coronary syndrome (ACS) patients and who undergo a percutaneous coronary intervention (PCI).[2,3] DAPT prevents restenosis and other secondary major adverse cardiac events (MACE) such as myocardial infarction (MI) and stroke.[4,5] Until 2009, the $P2Y_{12}$ inhibitor of choice was clopidogrel. However, genetic changes to the CYP 2C19 gene affects a patient's ability to metabolize clopidogrel, a prodrug, into its active form that leads to heterogeneity of treatment effects (HTE).[6] Pharmacogenetic tests now exist that may be able to

determine which patients would be appropriate candidates for clopidogrel use.[7] However, there is a lack of consensus in the use of the genetic test due to generalization of the test, absence of insurance coverage leading to out-of-pocket costs to the patient, and most importantly, no clear randomized trial evidence nor support from the national clinical guidelines.[1,7-10]

Two newer $P2Y_{12}$ inhibitors prasugrel and ticagrelor were approved in 2009 and 2011, respectively.[11,12] While prasugrel is also a prodrug, there were fewer concerns with the metabolism to its active metabolite, and it demonstrated significant improvements compared to clopidogrel for MACE in randomized trials, likely due to stronger inhibition of the $P2Y_{12}$ site.[13,14] Ticagrelor did not require metabolism and also demonstrated better outcomes compared to clopidogrel in randomized trials.[15] Similar results supported use of these newer $P2Y_{12}$ inhibitors in comparative effectiveness research (CER) studies and meta-analyses.[16-18]

While the newer $P2Y_{12}$ inhibitors showed better efficacy and effectiveness outcomes, safety was a concern as major bleeding rates were significantly higher compared to clopidogrel.[13,15] Clinicians have to balance effectiveness and safety possibilities for each individual patient in actual practice. While clinical trials and traditional comparative effectiveness studies addressed the heterogeneity of treatment effects through subgroup analysis, they are not nuanced enough to discover the optimal treatments for individual patients. Physicians are aware that this average treatment effect (ATE) from trials may not be applicable to all individual patients, and as a result, they attempt to make the best treatment choice possible by balancing formal study results, clinical judgement, and past experiences with patients.[19] This phenomenon has been studied previously and is an empiric measurement of patients and physicians "learning by doing"

through repeated personal trials with interventions and acquired knowledge.[20] Recent advancements in econometric methods using instrumental variables (IV) have allowed heterogenous treatment effects to be studied by obtaining person-centered treatment effects to assess the degree to which physicians are individualizing care through personalized prescribing.[20-22] Previous studies have used IV techniques to address measured and unmeasured confounders in this clinical space, but it is our understanding that this is the first study to fully address if physicians' prescribing patterns change from recognizing and learning from HTE of $P2Y_{12}$ inhibitors. The aim of this study was to examine physicians' prescribing patterns with $P2Y_{12}$ inhibitors to individualize care in the context of HTE.

Methods

Study design, study population, and data source

We used a retrospective cohort design using commercial claims and encounters data from IBM® MarketScan® Research Databases from 2010-2017. Patients greater than 18 years of age were identified as having an index event if they had an incident PCI. We excluded patients who had a prior PCI or coronary artery bypass graft (CABG) in the year prior. In order to measure this and to identify outcomes in the one year after PCI, patients were required to have continuous enrollment for one-year pre and post-index event. Patients were then excluded if they did not have an incident prescription fill for a $P2Y_{12}$ inhibitor 90 days pre- through 30 days post- PCI, a criterion used previously in this clinical setting.[23] Baseline covariates were collected in the one-year pre-index period and patients were followed up for effectiveness and safety outcomes in the

one-year post-index period. The University of Washington Institutional Review Board approved a waiver for the study as the data were deidentified.

The treatment variable was newer P2Y12 inhibitor (vs. clopidogrel). The method used in this study used a latent utility model that imposed a binary choice, and as a result the treatment variable could not be specified in more detail to prasugrel or ticagrelor. From a clinical perspective, clopidogrel is still used most often, and so the first decision choice a physician makes is whether to prescribe clopidogrel or one of the newer P2Y12 agents.[24] The effectiveness outcome was operationalized as revascularization and MACE, which encompassed in-hospital mortality, myocardial infarction, and stroke using International Classification Disease ninth revision Clinical Modification (ICD-9CM) and tenth revision (ICD-10CM) codes. All-cause mortality was not available from the data. The safety outcome of major bleed was identified using ICD-9CM and ICD-10CM codes from a previously published study using the same data.[25]

Baseline covariates included age, gender, insurance type, the Charlson Comorbidity Index (CCI), Elixhauser comorbidities, dyslipidemia, anticoagulant indication, HAS-BLED score, PCI indication (STEMI, NSTEMI, unstable angina, stable angina), stent type, and baseline healthcare utilization (emergency department, inpatient, outpatient). Dyslipidemia was defined as having at least one relevant diagnosis code and one prescription fill for an anti-cholesterol medication in the baseline period. Anticoagulant indication was identified if patients had diagnosis codes for pulmonary embolism, deep vein thrombosis, and atrial fibrillation as this variable could be associated with both the effectiveness and safety outcome. For PCI indication, patients who were not identified as having STEMI or NSTEMI were assumed to have unstable angina.

Statistical Analysis

We used an instrumental variable (IV) approach to control for observed and unobserved confounders in the study. The IV used was the frequency with which a patient's metropolitan statistical area (MSA) used newer P2Y12 inhibitors during the 6 months prior to a patient's index date. After controlling for year and MSA-level fixed effects, in order to control for overall clinical practice trends and area level confounders, the exogenous variation in treatment choices over time was exploited by the differential growth in 6-months-lagged MSA-level $P2Y_{12}$ inhibitors use (IV) over time across MSAs.

A limitation with traditional IV analysis is that the resultant treatment effect parameter, the local average treatment effect (LATE), is for a group of unidentifiable patients in the data set. This is because the LATE is only for those patients who would have changed their treatment choice only if their level of IV changed, which is an action that is not identifiable to the analyst. In order to further characterize the treatment effects to specific patients in a data set, local IV methods were developed that utilize treatment choice information across the distribution of a continuous IV by imposing a latent utility model.[26] Without loss of generalization, it is assumed that a positive latent utility indicates that patients receive P2Y12 inhibitors over clopidogrel. Through this model, marginal patients are identified who are indifferent to receiving P2Y12 inhibitors or clopidogrel because their observed characteristics (observed confounders and IV level) "balances" against their unobserved confounders such that their latent utility is zero. A small nudge/perturbation to the IV level (Figure 1.1), which by definition can move independent of all other confounders, would change their treatment choice. Consequently, comparing outcomes

across small changes in the IV level produces estimates of the treatment effects for these marginal patients (called the marginal treatment effects). Varying the level of the continuous IV can produce the marginal treatment effects for different marginal patients with different levels of observed and unobserved confounder levels

Approach to Estimating PeT effects using the IV Design

Since for each patient in our sample we know the treatment choice one has made and their observed confounder levels, we can identify the levels of unobserved confounders that would conform with the treatment choice (based on the latent utility model) and average the MTEs estimated over those levels of unobserved confounders to form a person-centered treatment (PeT) effect.[21] PeT effects are easy to interpret as they are the individualized treatment effects conditional on a patient's observed risk factors and averaged over that patient's individualized unobserved risk factors that conform to one's choice. PeT effects can be averaged over any observed factors to obtain an overall or subgroup-level mean treatment effect estimate. For further clarification of the LIV method used, MTEs, and PeT effects, please see Appendix A.1.1.

Logistic regression models were used to obtain the PeT effects for effectiveness and safety. Both outcome measures were reported as mean (95% CI) differences in the absolute risk of MACE/revascularization and major bleed. By measuring both PeT effects for effectiveness and safety, optimal treatments could be identified for patients by determining which treatment would produce the best effectiveness and safety outcomes. SAS (version 9.4; SAS Institute) and Stata (version 13.1; StataCorp LP) were used for data collection and analyses.

Results

A total of 66,001 patients were identified through the inclusion and exclusion criteria. This population was reduced to the central 80% (n=52,823) of the IV where there was variation and enough of a sample size. Unadjusted baseline characteristics revealed patients on newer P2Y12 inhibitors were generally younger and had fewer comorbidities (Table 1.1). The strength of the IV was assessed and considered strong (*F* statistic, 20.41), and the IV demonstrated a reduction in baseline covariate imbalance for predicted residuals across the median IV level compared to across treatment (Figures 1.2 and 1.3). Furthermore, our instrument passed a falsifiability test by showing no difference in pneumonia outcomes across levels of IV (p=0.77).[16]

In the overall study period, the estimated risk difference for the effectiveness outcome was a 3.97 percentage point reduction (95% CI, -6.97 to -0.26) and a 2.93 percentage point reduction (95% CI, -4.83 to -0.70) for the safety outcome, both of which favored the newer P2Y12 inhibitors (Table 1.2). These effects generally held constant across the study period (Figures 1.4 and 1.5). The average treatment effect on the treated showed that the significant risk reduction in MACE improved slightly from 2010 to 2013 but trended in the opposite direction afterwards.

Subgroup analysis showed a significant 8.95 percentage point MACE risk reduction (95% CI, 1.48 to 14.75) for STEMI patients initiating newer P2Y12 inhibitors and a significant 4.74 percentage point reduction (95% CI, 0.52 to 8.30) for patients initiating newer P2Y12 inhibitors under 55 years of age (Figure 1.6). Patients who had a drug-eluting and bare-metal stent also showed significant improvement in effectiveness. For major bleed, patients with STEMI,

NSTEMI, diabetes, DES, and BMS had significantly lower risk when initiating newer P2Y12 inhibitors (Figure 1.7).

There was variability in PeT effects for effectiveness and safety for both newer P2Y12 and clopidogrel users (see Figure 1.8). Throughout the study period, around 80% of patients who initiated on prasugrel and ticagrelor were optimally matched, meaning they obtained the most benefit in effectiveness and safety compared to if they had been prescribed clopidogrel (Figure 1.9). Among clopidogrel initiators, the proportion of patients whose optimal therapy would have been the newer $P2Y_{12}$ inhibitors showed a downward trend from 82.61% in 2010 to 73.60% in 2015 (Figure 1.10).

If all patients initiated treatment on prasugrel or ticagrelor, the predicted probability of MACE and revascularization would have been 16.9% while major bleed would have been 11.6% (Table 1.2), both significant improvements over current clinical practice. If all patients started on clopidogrel, both the effectiveness and safety outcomes would have increased relative to the status quo of targeted prescribing patterns by 8.29% and 8.21%, respectively, although significance was not reached. If all patients were matched to the antiplatelet that produced the most beneficial effectiveness and safety effects, we estimated the outcomes under these ideal scenarios to significantly lower the predicted probability of MACE and revascularization to 15.9% (95% CI, 14.3% to 18.4%) and major bleed to 11.1% (95% CI, 9.9% to 12.4%).

Discussion

Our analysis revealed the ATE for the effectiveness outcome was statistically significantly better for the newer P2Y12 inhibitors compared to clopidogrel throughout the treatment period. Better

effectiveness outcomes for newer P2Y12 inhibitors are in line with results from previous CER studies.[16,17] The safety outcome marginally favored the newer P2Y12 inhibitors throughout the study period. This finding contrasted with those found in RCTs.[13,15] However, this could be due to a homogenous and older population in the clinical trials, which contrasts with our more heterogenous, younger population. Furthermore, previous CER studies also found safety with prasugrel or ticagrelor to be nonsignificant compared to clopidgorel.[16,18,27] The significant safety difference in our study compared to previous CER studies could be due to our analysis fully accounting for heterogeneity of treatment effects and accounting for unobserved confounders. Similarly, when assessing effectiveness and safety results by subgroup analysis, while some results were consistent (e.g. patients with STEMI, NSTEMI, DES, and BMS) for effectiveness, safety outcomes favored prasugrel or ticagrelor in contrast to the clinical trials.

Not surprisingly, there was considerable HTE with these antiplatelet medications (Figure 4), and we found trends that indicated adjusting targeted treatment over time for the studied antiplatelet medications as physicians seemed to change prescribing patterns with experience. With the newer $P2Y_{12}$ inhibitors, the results suggested physicians prescribing patterns held generally constant, especially when assessed in terms of MACE reduction. For patients initiated on clopidogrel, our study implied from the prescribing patterns that physicians targeted patients who might not benefit as much from the newer $P2Y_{12}$ inhibitors. These shifts in clinical practice might reflect the implications from CER studies that while prasugrel and ticagrelor are more effective than clopidogrel in reducing MACE, the safety profile of the newer $P2Y_{12}$ inhibitors has a mixed signal.

There are also several policy implications with our study. Currently, the clinical guidelines advocate the use of newer $P2Y_{12}$ inhibitors, specifically ticagrelor, over clopidogrel.[3] In that scenario, both effectiveness and safety outcomes would have significantly improved in our patient population. A health plan perspective would advocate the use of clopidogrel for their enrollees as its generic status makes it preferable for a tiered formulary. In this scenario, there would be a higher, albeit not significant, probability of both MACE and major bleeding. Most interestingly, if patients' optimal therapy could be known, perhaps with the help of a validated pharmacogenetic test, a further improvement in MACE and major bleeding could be achieved. While this is a lofty ambition to perfectly predict optimal treatment, it should be the goal of personalized medicine. While conflicting opinions currently exist regarding pharmacogenetic testing in this area, future studies are needed to assess its applicability.

Our study has several strengths. We used a novel IV method to examine HTE, clinical practice adjusting to HTE, and possible policy implications of leveraging approaches to improve personalized medicine. We believe our study is the first to study these phenomena in the context of P2Y12 inhibitors. Similar to other studies using an IV approach in this clinical area, we believe our IV to be strong and valid, while also passing a falsifiability test where previous studies failed.

This study also has limitations. While we believe our IV approach to be sound methodologically, the assumptions of exogeneity condition and exclusion restriction of IV analysis are not directly testable. MarketScan as a dataset also has the limitation of not having all-cause mortality data which would have been clinically meaningful. However, as we only used the commercial claims

database, loss of follow-up due to death outside of the hospital setting within the one-year follow-up period is less of a concern compared to studies done in a more elderly population. Furthermore, as aspirin claims are sparse in MarketScan, likely due to out-of-pocket cash purchase by patients, we assume patients are compliant with aspirin medication use as part of DAPT.

In the absence of identifiable characteristics of HTE for P2Y12 inhibitors, physicians' prescribing patterns changed with time, possibly indicating improvement of targeting care with these antiplatelet agents. With continued use of these medications, physicians may have learned which patients would benefit most from clopidogrel or one of the newer agents. Clinical practice and patient outcomes could improve if prescribing patterns were guided by mechanisms to identify factors that affect treatment effect heterogeneity.

Tables and Figures

Table 1.1. Baseline characteristics

Variable	Clopidogrel (n=33,496)	Newer P2Y12 (n=19,322)	P value	Standardized difference across treatment	Standardized difference across IV
Age, mean (SD)	55.16 (6.53)	54.38 (6.74)	<0.001	0.0434	0.0032
Male, n (%)	25498 (76.1)	15194 (78.6)	<0.001	0.0258	0.0029
Fee-for-service, n (%)	28209 (84.2)	16769 (86.8)	<0.001	0.0207	0.0018
Incident PCI inpatient setting, n (%)	21571 (64.4)	13164 (68.1)	<0.001	0.0370	0.0025
Incident PCI drug-eluting stent, n (%)	12196 (36.4)	8033 (41.6)	<0.001	0.0205	0.0003
Incident PCI bare metal stent, n (%)	19374 (57.8)	10641 (55.1)	<0.001	0.0044	0.0008
Incident PCI due to STEMI, n (%)	18561 (55.41)	11920 (61.69)	<0.001	0.0518	0.0016
Incident PCI due to NSTEMI, n (%)	14449 (43.14)	7220 (37.37)	0.89	0.0026	0.0019
Incident PCI due to unstable angina, n (%)	486 (1.45)	182 (0.94)	<0.001	0.0958	0.0019
Baseline outpatient visits, mean (SD)	4.18 (13.38)	3.25 (10.73)	<0.001	0.0280	0.0025
Baseline inpatient visits, mean (SD)	0.03 (0.25)	0.02 (0.19)	<0.001	0.0193	0.0003
Baseline ER visits, mean (SD)	0.09 (0.62)	0.07 (0.59)	0.002	0.0112	0.0026
Charlson comorbidity index, mean (SD)	1.67 (1.92)	1.49 (1.69)	<0.001	0.0521	0.0002
Anticoagulant indication, n (%)	2784 (8.3)	1101 (5.7)	<0.001	0.0409	0.0018
Hyperlipidemia, n (%)	19272 (57.5)	10416 (53.9)	<0.001	0.0322	0.0004
Valvular disease, n (%)	2000 (6.0)	941 (4.9)	<0.001	0.0279	0.0007
Hypertension, n (%)	17912 (53.5)	9846 (51.0)	<0.001	0.0380	0.0041
Chronic pulmonary disease, n (%)	3185 (9.5)	1665 (8.6)	<0.001	0.0221	0.0005
Diabetes without complications, n (%)	7798 (23.3)	4245 (22.0)	<0.001	0.0235	0.0032
Diabetes with complications, n (%)	2061 (6.2)	984 (5.1)	<0.001	0.0249	0.0011
Hypothyroidism, n (%)	2588 (7.7)	1471 (7.6)	0.64	0.0106	0.0003
Obesity, n (%)	4278 (12.8)	2473 (12.8)	0.93	0.0151	0.0019
Fluid & electrolyte disorders, n (%)	2706 (8.1)	1301 (6.7)	<0.001	0.0279	0.0055
Deficiency anemias, n (%)	2415 (7.2)	1101 (5.7)	<0.001	0.0330	0.0005
Depression, n (%)	1997 (6.0)	1018 (5.3)	<0.001	0.0176	0.0023

Renal disease, n (%)	1763 (5.3)	692 (3.6)	<0.001	0.0350	0.0029
HAS-BLED score, mean (SD)	0.84 (0.83)	0.77 (0.77)	<0.001	0.0546	0.0013
Peripheral artery or vascular disease, n (%)	2308 (6.9)	1054 (5.5)	<0.001	0.0281	0.0022

Table 1.2. Effectiveness and safety outcomes in 12 months following initiation of antiplatelet therapy under various therapeutic scenarios

	Effectiveness			Safety		
Scenario	Predicted probability of MACE	% change from status-quo	p-value	Predicted probability of major bleed	% change from status-quo	p-value
Status-quo	0.193 (0.189 - 0.196)	-		0.134 (0.131 - 0.137)	-	
All patients started on newer P2Y12 inhibitor	0.169 (0.154 - 0.187)	-12.43	<0.05	0.116 (0.105 - 0.127)	-13.43	<0.05
All patients started on clopidogrel	0.209 (0.190 - 0.224)	8.29	0.18	0.145 (0.134 - 0.153)	8.20	0.15
All patients started on optimal predicted therapy	0.159 (0.143 - 0.184)	-17.61	<0.01	0.111 (0.099 - 0.124)	-17.16	<0.01

Note: p-values reflect comparisons of predicted probability of events under various scenarios to status quo

Figure 1.1. Identification of the marginal treatment effect

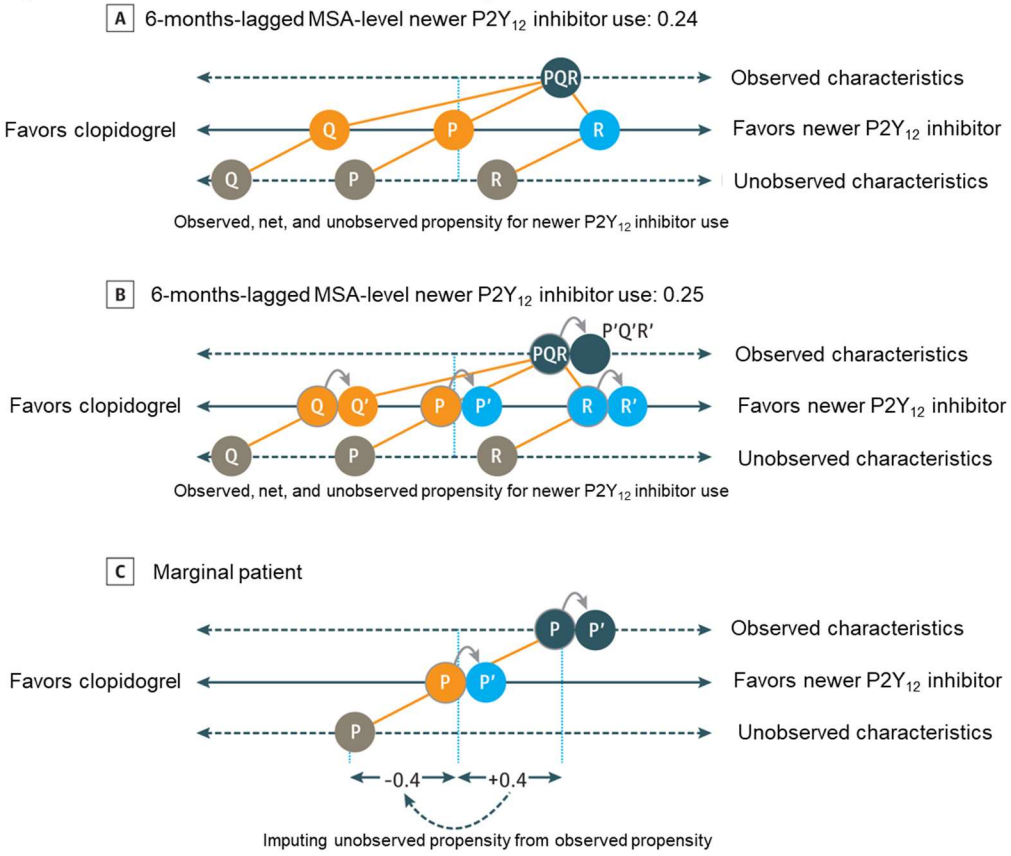


Figure 1.2. Covariate imbalance across treatment

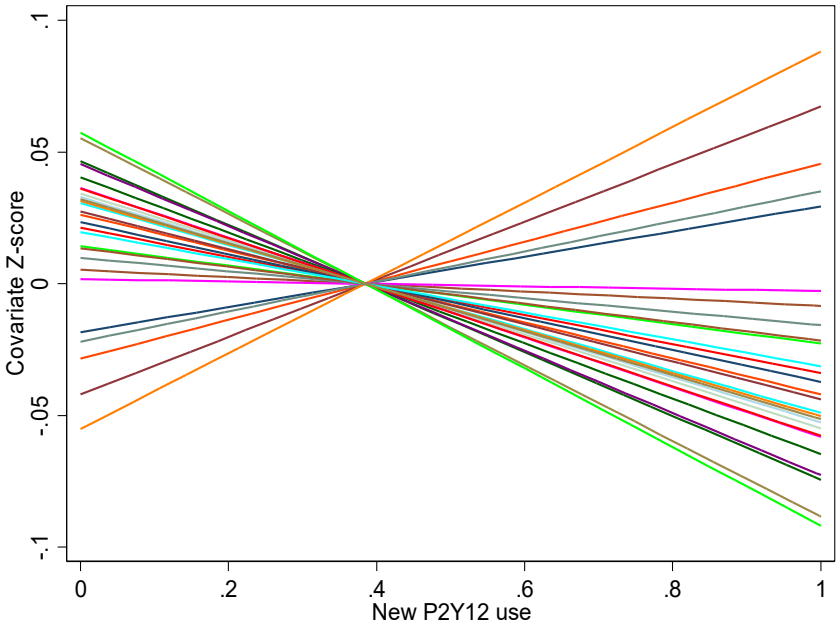


Figure 1.3. Covariate imbalance across instrumental variable

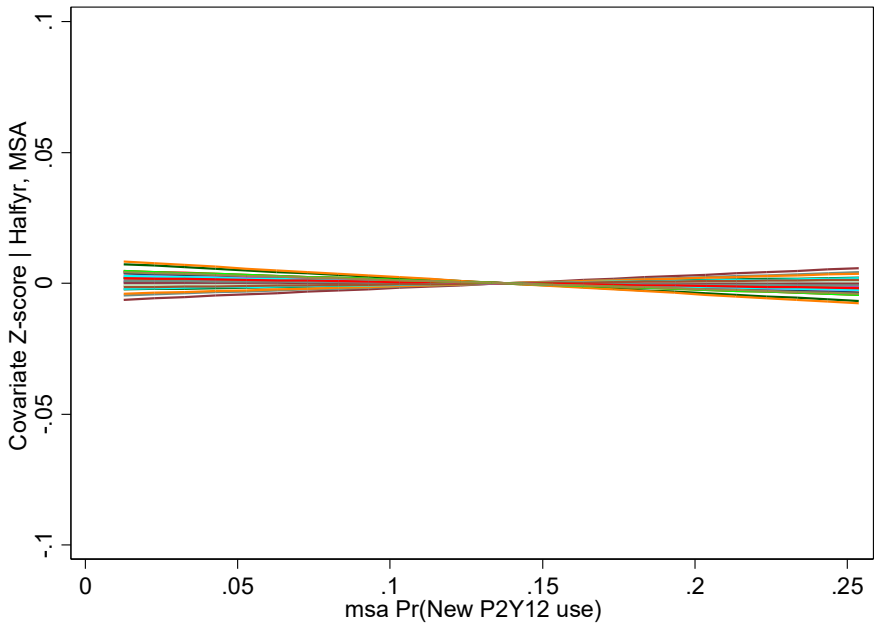


Figure 1.4. Average treatment effects of effectiveness

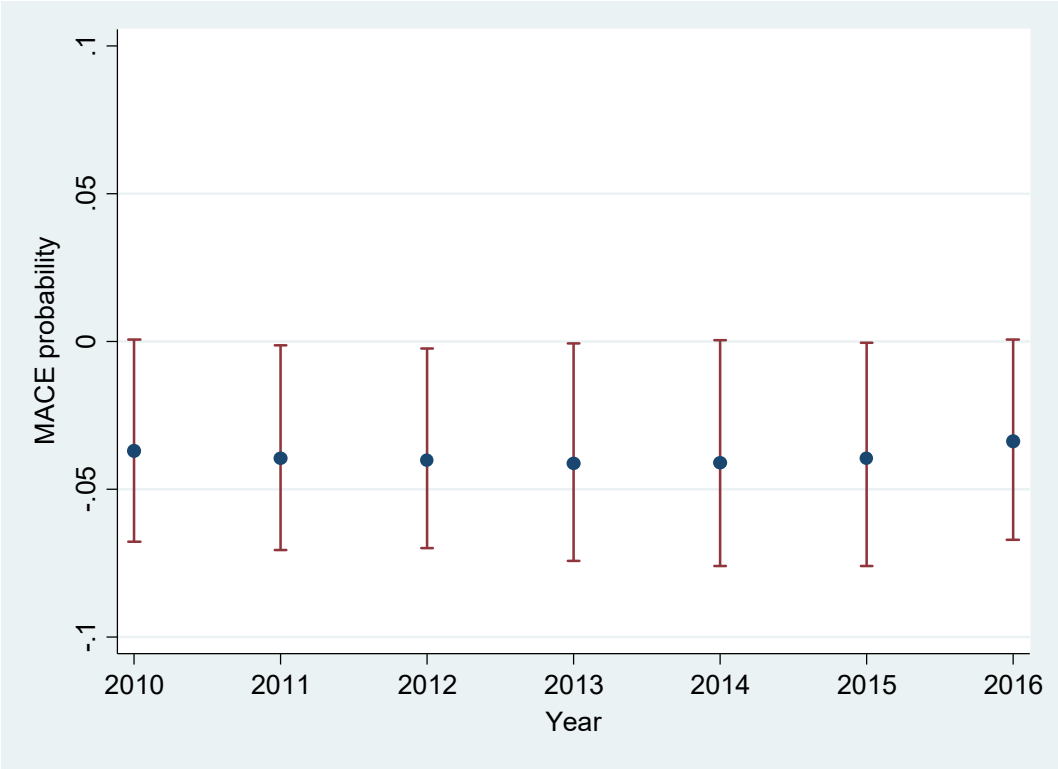


Figure 1.5. Average treatment effects of safety

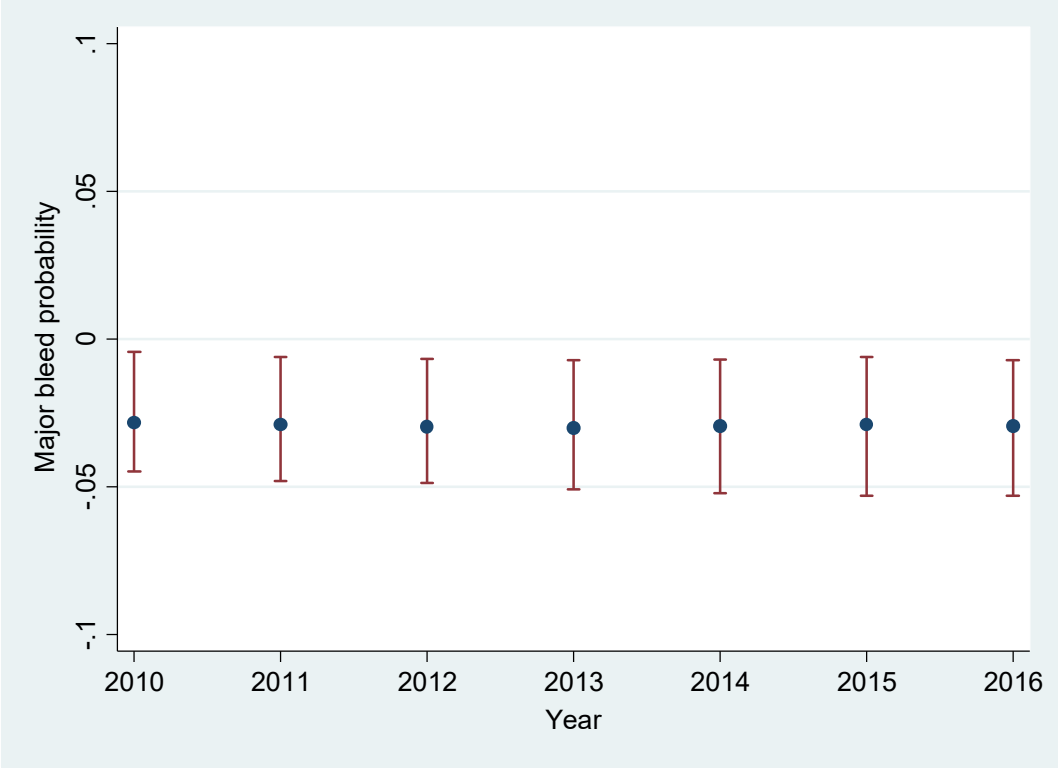


Figure 1.6. Subgroup analysis of MACE outcomes

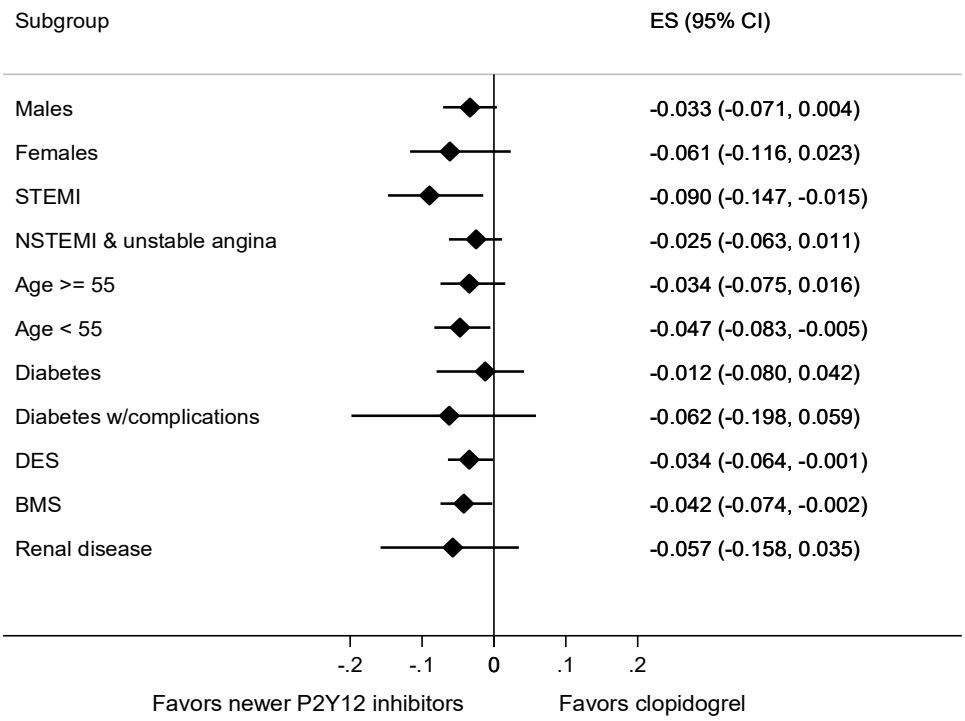


Figure 1.7. Subgroup analysis of major bleeding outcomes

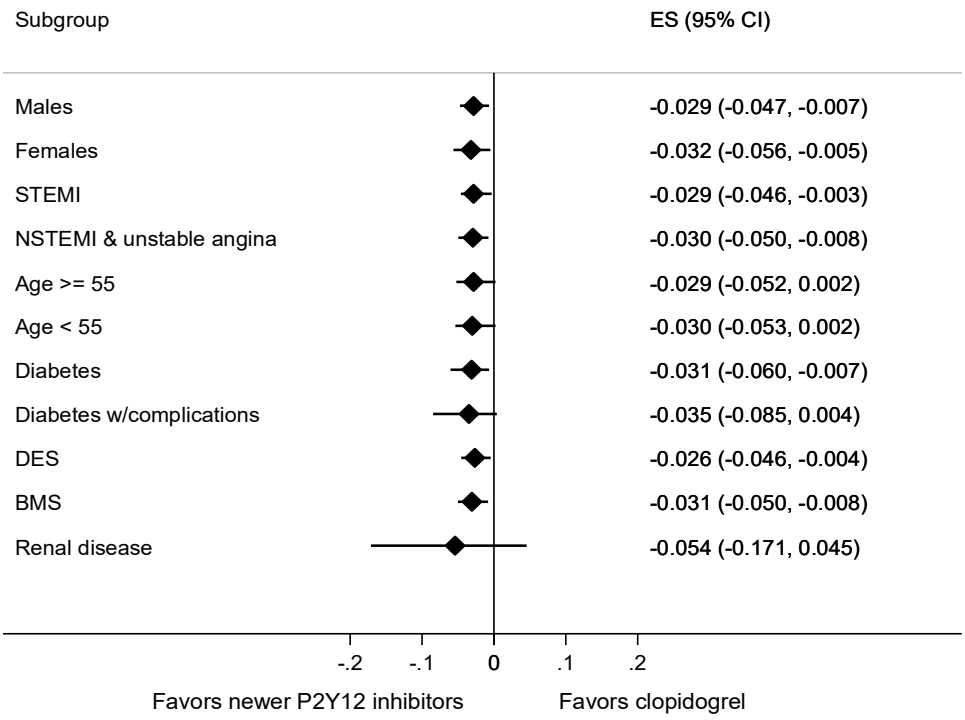


Figure 1.8. Heterogeneity of treatment effects of $P2Y_{12}$ inhibitors

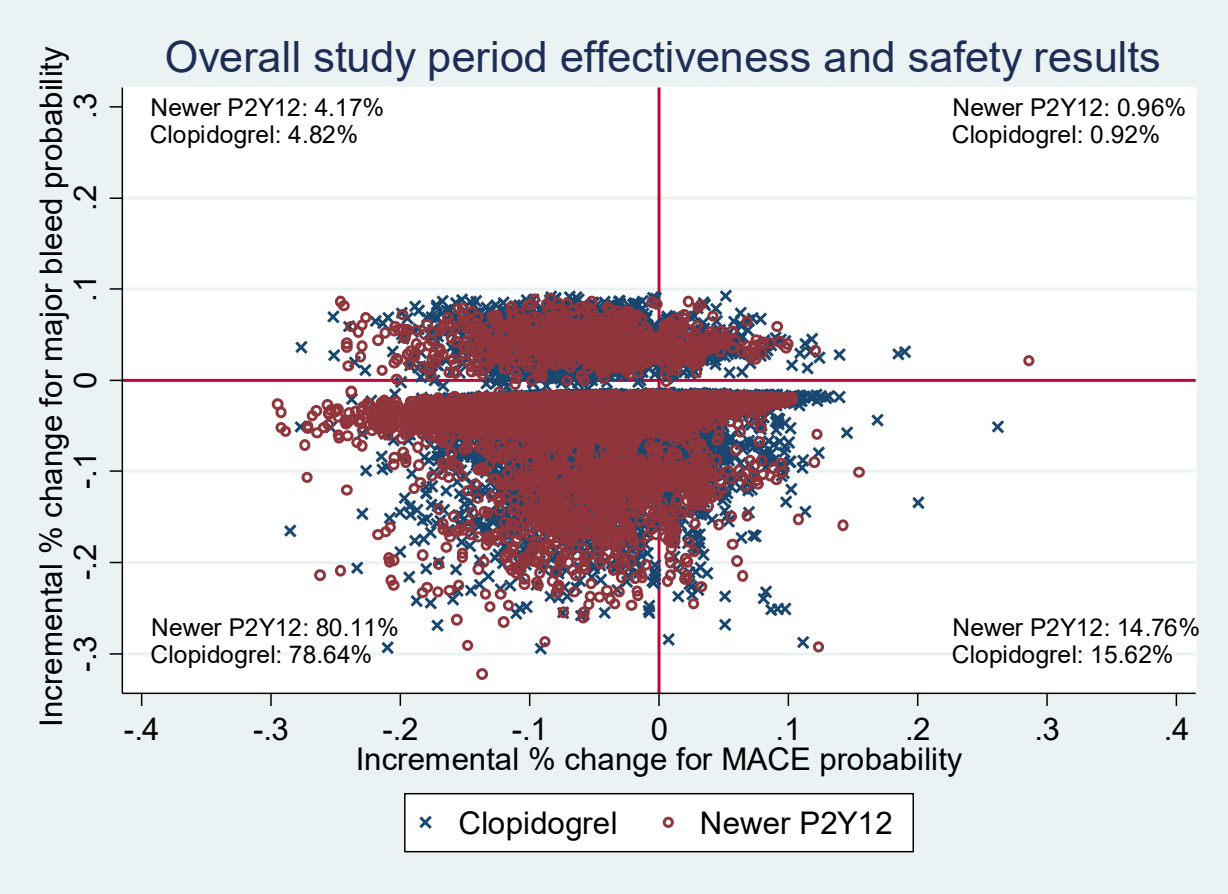


Figure 1.9. Targeted treatment of newer P2Y$_{12}$ inhibitor initiators

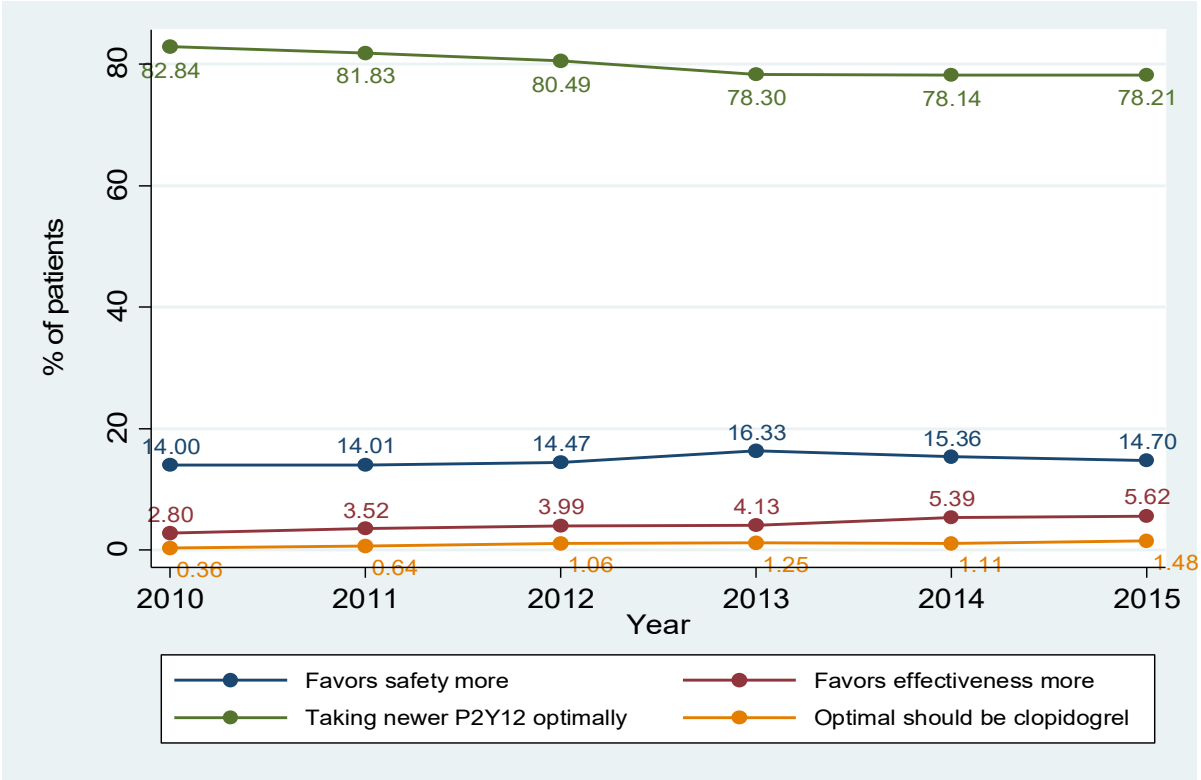
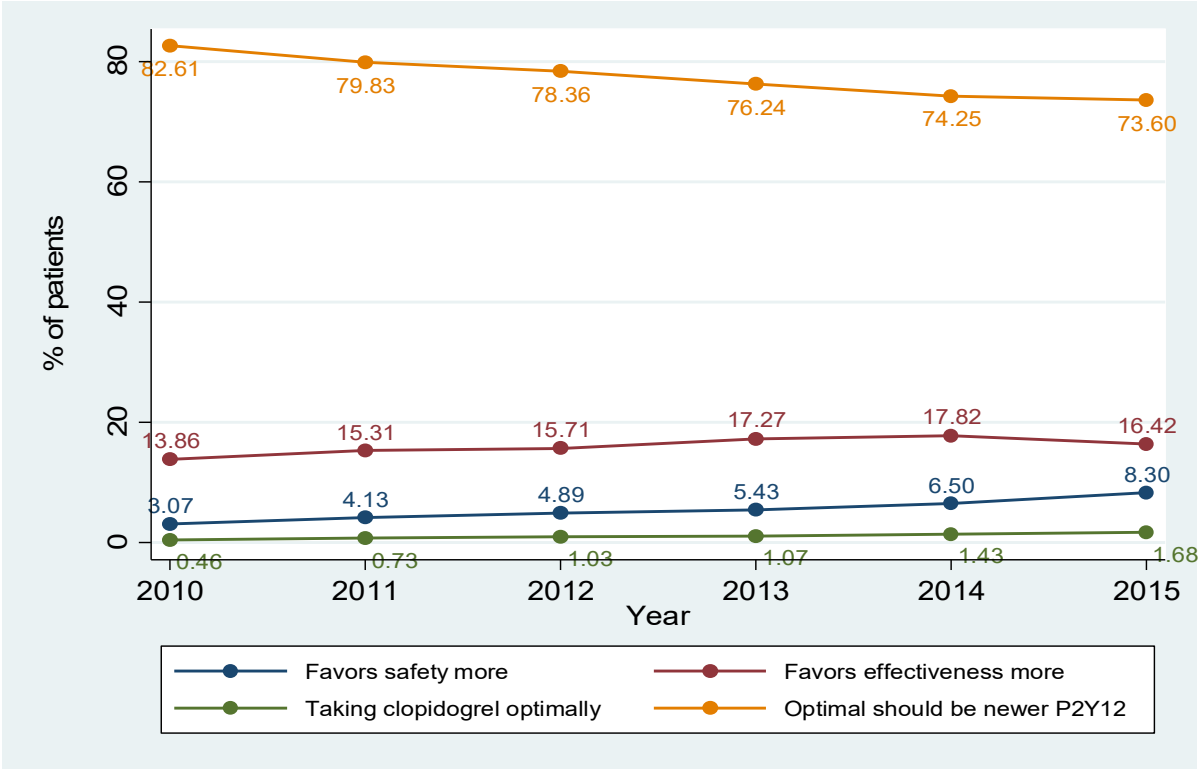


Figure 1.10. Targeted treatment of clopidogrel initiators



References

1. Amsterdam E, Wenger N, Brindis R, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;130(25):e344-426.
2. Levine G, Bates E, Blankenship J, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *Circulation.* 2016;133(11):1135-1147.
3. Levine G, Bates E, Bittl J, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation.* 2016;134(10):e123-155.
4. Mehta S, Yusuf S, Peters R, Bertrand M, Lewis B, Natarajan M. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet.* 2001;358(9281):527-533.
5. Yusuf S, Zhao F, Mehta S, Chrolavicius S, Anand S. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001;345:494-502.
6. Steinhubl S, Berger P, Mann JI, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA.* 2002;288:2411-2420.
7. Knauer M, Diamandis E, Hulot J, Kim R, So D. Clopidogrel and CYP2C19: pharmacogenetic testing ready for clinical prime time? *Clin Chem.* 2015;61(10):1235-1240.
8. Bhopalwala A, Hong R, Khan Z, Valentin M, Badawi R. Routing screening for CYP2C19 polymorphisms for patients being treated with clopidogrel is not recommended. *Hawaii J Med Public Health.* 2015;74(1):16-20.
9. Holmes D, Dehmer G, Kaul S, Leifer D, O'Gara P. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association. *J Am Coll Cardiol.* 2010;56(4):321-341.
10. Levine G, Jeong Y, Goto S, et al. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol.* 2014;11(10):597-606.
11. Effient [package insert]. Eli Lilly and Company, Indianapolis, IN; 2019.
12. Brilinta [package insert]. AstraZeneca Pharmaceuticals LP, Wilmington, DE; 2019.
13. Wiviott S, Braunwald E, McCabe C, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001-2015.
14. Zhang L, Lu J, Dong W, et al. Meta-analysis of comparison of the newer P2Y12 inhibitors (oral preparation or intravenous) to clopidogrel in patients with acute coronary syndrome. *J Cardiovasc Pharmacol.* 2017;69:147-155.
15. Wallentin L, Becker R, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045-1057.

16. Federspiel J, Anstrom K, Xian Y, et al. Comparing inverse probability of treatment weighting and instrumental variable methods for the evaluation of adenosine diphosphate receptor inhibitors after percutaneous coronary intervention. *JAMA Cardiol.* 2016;1(6):655-665.
17. Kim K, Lee T, Ardati A, DiDomenico R, Touchette D, Walton S. Comparative effectiveness of oral antiplatelet agents in patients with acute coronary syndrome. *Pharmacotherapy.* 2017;37(8):877-887.
18. Singh S, Singh M, Grewal N, Khosla S. Comparative efficacy and safety of prasugrel, ticagrelor, and standard-dose and high-dose clopidogrel in patients undergoing percutaneous coronary intervention: a network meta-analysis. *American Journal of Therapeutics.* 2016;23:e52-e62.
19. Garber A, Tunis S. Does comparative-effectiveness research threaten personalized medicine? *N Engl J Med.* 2009;360(19):1925-1927.
20. Basu A, Jena A, Goldman D, Philipson T, Dubois R. Heterogeneity in action: the role of passive personalization in comparative effectiveness research. *Health Econ.* 2014;23(3):359-373.
21. Basu A. Estimating person-centered treatment (PeT) effects using instrumental variables: an application to evaluating prostate cancer treatments. *J Appl Econ (Chichester Engl).* 2014;29(4):671-691.
22. Basu A, Gore J. Are elderly patients with clinically localized prostate cancer overtreated? Exploring heterogeneity in survival effects. *Medical Care.* 2015;53:79-86.
23. Dayoub E, Seigerman M, Tuteja S, et al. Trends in platelet adenosine diphosphate P2Y12 receptor inhibitor use and adherence among antiplatelet-naive patients after percutaneous coronary intervention, 2008-2016. *JAMA Intern Med.* 2018;178(7):943-950.
24. Desai R, Spoendlin J, Mogun H, Gagne J. Contemporary time trends in use of antiplatelet agents among patients with acute coronary syndrome and comorbid diabetes mellitus or chronic kidney disease. *Pharmacotherapy.* 2017;37(10):1322-1327.
25. Lip G, Pan X, Kamble S, et al. Major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban or warfarin: a “real-world” observational study in the United States. *Int J Clin Pract.* 2016;70(752-763).
26. Heckman J, Vytlacil E. Local instrumental variables and latent variable models for identifying and bounding treatment effects. *Proc Natl Acad Sci.* 1999;96(8):4730-4734.
27. Spoendlin J, Gagne J, Lewey J, Patorno E, Schneeweiss S, Desai R. Comparative effectiveness and safety of antiplatelet drugs in patients with diabetes mellitus and acute coronary syndrome. *Pharmacoepidemiol Drug Saf.* 2018;27(12):1361-1370.

Chapter 2: Examining the cost-effectiveness of empirical passive personalization with $P2Y_{12}$ inhibitors in patients with acute coronary syndrome

Abstract

Importance: In Aim 1, universally treating patients with a newer $P2Y_{12}$ inhibitor demonstrated effectiveness compared to clopidogrel or current targeted prescribing of any of the three antiplatelet agents based on patient characteristics. However, given the higher cost and potential safety concerns of the newer $P2Y_{12}$ inhibitors, the potential cost-effectiveness of this universal treatment strategy compared to current prescribing patterns is unknown.

Objective: To estimate the potential cost-effectiveness of empirical targeted prescribing compared to universal use of either clopidogrel or a newer $P2Y_{12}$ inhibitor for the secondary prevention of major cardiac adverse events.

Design, Setting, and Participants: We constructed a hybrid model (1-year and lifetime) to estimate costs and outcomes for patients after recent acute coronary syndrome and percutaneous coronary intervention. Inputs for first year of the model were based on Aim 1 using IBM® MarketScan® data that showed significant improvement in major adverse cardiovascular events for treatment with a newer $P2Y_{12}$ inhibitor compared to targeted prescribing or clopidogrel. Sources and long-term model inputs were derived from the literature. Patients were assumed to take their $P2Y_{12}$ inhibitor for the guideline-based 1-year after acute coronary syndrome (short term model) and then returned to aspirin monotherapy. We used a healthcare payer perspective, discounted costs and outcomes at a rate of 3%, and adjusted costs to 2019 US dollars.

Exposure(s): Targeted prescribing of clopidogrel, prasugrel, and ticagrelor vs. universal clopidogrel vs. universal newer $P2Y_{12}$ inhibitor

Main Outcome(s) and Measure(s): Lifetime costs, life years (LYs) and quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratio (ICER)

Results: Targeted prescribing resulted in 11.63 LYs, 9.92 QALYs, and $72,402 total costs; universal clopidogrel resulted in 11.59 LYs, 9.84 QALYs, and $72,670 total costs; universal newer $P2Y_{12}$ inhibitors resulted in 11.67 LYs, 10.00 QALYs, and $73,325 total costs. Targeted prescribing was a dominant strategy compared to universal clopidogrel treatment. However, universally treating patients with a newer $P2Y_{12}$ inhibitor compared to current targeted prescribing was a cost-effective strategy with an ICER of $11,144/QALY. These results were robust in one-way and probabilistic sensitivity analyses.

Conclusions and Relevance:

Universal treatment with newer $P2Y_{12}$ inhibitors, as advocated by current clinical guidelines, is a cost-effective approach compared to current clinical practice. Future studies assessing the potential cost-effectiveness of a more personalized approach to treatment, such as pharmacogenetic-guided therapy, would be beneficial.

Background

Cost-effectiveness analysis (CEA) is a mechanism to approximate the value of pharmaceutical treatment, especially for new drugs that are typically more costly than current standard of care or generic medications.[1] In the United States, CEA is not routinely or explicitly used for coverage and reimbursement decisions, but is nevertheless an important consideration for decision makers to compare costs and measures of effectiveness for different interventions.[2] Typically, CEA is carried out by using the average treatment effect (ATE) from clinical trials or observational studies to compare two or more interventions, which is a measure of the difference in outcomes for a treated and control group. The ATE would include, for example, the hazard ratio of one treatment compared to another and the corresponding confidence intervals. However, there has been a push to incorporate patient variability to treatment, known as heterogeneity of treatment effects (HTE) into CEA models, since the ATE is not applicable for all patients.[2-5] HTE studies inform at a subgroup level (e.g. gender, age, comorbidity), but ideally a model would be able to incorporate HTE at an individual patient level.

$P2Y_{12}$ inhibitors are a class of medications that have been associated with HTE.[6-8] These antiplatelet agents are guideline-based therapy for acute coronary syndrome and percutaneous coronary intervention to prevent secondary myocardial infarction (MI) and cardiovascular death.[9-11] Generally, clinicians adapt prescribing patterns through learning which medications might work best for an individual through experience in similar patients, a process termed passive personalization (PP) in the literature.[12]

In Aim 1, our group assessed how physicians empirically apply this targeted prescribing with $P2Y_{12}$ inhibitors in patients with acute coronary syndrome (ACS).[13]). We used IBM® MarketScan® data and a novel instrumental variable method to assess effectiveness of these antiplatelet medications in reducing major adverse cardiovascular events (MACE) at the patient level. The newer $P2Y_{12}$ inhibitors significantly lowered MACE by 3.97 percentage points (i.e. the ATE) at 1-year follow-up compared to clopidogrel (95% CI, -6.97 to -0.26). However, we found considerable heterogeneity in treatment effects of clopidogrel and the newer $P2Y_{12}$ inhibitors, and we observed the trends in heterogeneity changing over time. This meant physicians were changing targeted prescribing to determine which drug would bring the most clinical effectiveness benefit to patients over time.

Previous CEA models have shown that the newer $P2Y_{12}$ inhibitors are likely cost-effective with incremental cost-effectiveness ratio (ICER) approximately ranging from $5,000 to $30,000 per quality-adjusted life-year (QALY) gained.[14-19] Another CEA showed genotype-driven antiplatelet therapy in the short-term could also be cost effective.[20] There have also been CEA that examine whether real-world clinical practice is cost-effective.[21,22] Bridging together these two concepts, we sought to model cost-effectiveness of clinical practice of prescribing clopidogrel or newer $P2Y_{12}$ inhibitors ticagrelor or prasugrel in the context of heterogeneity of treatment effects. The objective of this study was to assess the cost-effectiveness of empirical clinical practice of targeted prescribing versus universal clopidogrel or universal newer $P2Y_{12}$ inhibitors, and to determine the policy and clinical implications of the results.

Methods

Markov Model Overview

We developed a hybrid economic model that included a short-term (1-year) decision tree and a lifetime Markov model using Microsoft Excel (Redmond, WA, USA). The model used a US healthcare sector perspective. Both the short and lifetime model frameworks were based on previously published CEA studies.[13] The 1-year decision tree was initiated by patients who underwent PCI and then could enter one of three interventions: empirical targeted prescribing informed by current clinical practice, universal treatment with a newer $P2Y_{12}$ inhibitor (ticagrelor or prasugrel), or universal treatment with clopidogrel (Figure 2.1). Patients received the $P2Y_{12}$ inhibitor for the full year. If the patients went through the targeted prescribing decision node, they were prescribed what the physician deemed best for them in terms of effectiveness and safety. Patients would then experience one of the following outcomes: no further event, revascularization, non-fatal (MI), non-fatal stroke, and death from any cause. In the base case analysis, Aim 1 informed the proportion of patients receiving each $P2Y_{12}$ inhibitor (Table 2.1).

At the end of the 1-year decision tree, patients entered the Markov model in the appropriate health state (Figure 2.2). Similar to previous CEAs, patients who experienced revascularization or no event in the 1-year decision tree were grouped together. Patients who experienced non-fatal MI and non-fatal stroke remained in that state for a year and then transitioned to their respective post MI/stroke-health states. We applied a discount rate of 3%, used yearly cycles, used half-cycle corrections, and a lifetime time horizon. All costs were adjusted and reported in 2019 US dollars using the medical care consumer price index. The results were reported as costs per life-year (LY) gained and cost per quality-adjusted life-year (QALY) gained.

Clinical Inputs

Clinical inputs and transition probabilities are detailed in Table 2.1. Patients entered the 1-year model at the age of 55, which was the average age in Aim 1. Patients that entered the targeted prescribing arm had a 63% chance of being prescribed clopidogrel, a 29% chance of prasugrel, and an 8% chance of ticagrelor. While the proportion of patients on prasugrel and ticagrelor could be estimated and used separately for cost purposes, the 1-year clinical probabilities were a combined estimate as the methods from Aim 1 imposed an explicit binary treatment choice (i.e. newer $P2Y_{12}$ inhibitor versus clopidogrel). Also, since our previous analysis used MarketScan®, which does not have mortality data, we used a 1-year fatal MI and stroke probability from the literature.[23]

The transition probabilities in the Markov model were informed by the literature in this clinical setting.[17,24,25] While previous studies did not allow patients in the post-health states to experience the other clinical event, we felt this did not accurately reflect possible outcomes, and thus allowed this possibility. Furthermore, MI and stroke-specific hazard ratios for an increased risk of death in the health states were applied to the US background mortality rate.[17]

Adverse Events

The main serious adverse events for $P2Y_{12}$ inhibitors are bleeding complications. Bleeding probabilities were taken from package inserts for the model[26].[27]. For clopidogrel, the ticagrelor US product monograph was used for bleeding rates. For prasugrel, the prasugrel US product

monograph was used but the bleed rates were adjusted based on clopidogrel's bleed rate in the ticagrelor product monograph for fairer comparison. The bleed rates were applied only to the 1-year short term model when patients were expected to take medication. No adjustment to the bleed rates from the product monograph were needed as the follow up period was similarly 1-year.

Quality-of-Life Inputs

The utility values used in the short and lifetime models were based off the literature.[14,28] Utility decrements were applied to both the non-fatal MI and non-fatal stroke states when patients experienced the events.

Cost Inputs

Pharmaceutical costs for the $P2Y_{12}$ inhibitors were taken from the federal supply schedule (FSS) as suggested by the 2nd Panel on CEA.[29,30] The FSS represents the costs paid by federal agencies in the US and are the lowest price offered by the pharmaceutical manufacturer.

Since bleeding adverse events require medical intervention, costs for these events were calculated from diagnosis related group codes (DRG). Minor bleeds were calculated by taking the average of intracranial and gastrointestinal hemorrhages without major complication or comorbidity (DRG 066 and 379), while major bleeds were averaged for those with major complication or comorbidity (DRG 064 and 377).

Costs for the 1-year model were generated from Aim 1. Clinical costs for the lifetime model were gathered from the literature. In the lifetime model, the no event health state cost was taken from the CEA conducted alongside the ticagrelor RCT, which was conducted from the perspective of Sweden.[17] To convert the currency used from this study (€), the purchasing price parity of the European Union was used and then updated to 2019 US dollars.

Sensitivity Analyses

To test the robustness of the two-part model, one-way sensitivity analysis and probabilistic sensitivity analysis were conducted. In the one-way sensitivity analysis, model parameters were varied between reasonable ranges based on confidence intervals or clinical judgment. The distributions of the parameters were based on recommended text.[31] In the probabilistic sensitivity analysis, we ran 5,000 simulations and created a cost-effectiveness acceptability curve to examine which treatment arm would be cost-effective at varying willingness-to-pay threshold ranges.

We also conducted a scenario analysis to evaluate the upper bound of how cost-effective current clinical practice of targeted prescribing could be by matching patients to their optimal $P2Y_{12}$ inhibitor, meaning they were prescribed the antiplatelet agent that would result in the lowest probability of a MACE outcome. We also tracked the cost-effectiveness of empirical targeted prescribing over time to assess whether adaptive changes in prescribing patterns improved with more familiarity in recognizing heterogeneity of treatment effects.

Model Validation

We validated the appropriateness of the conceptual model by using a structure from previously published studies and refined using expert clinical judgement.[32] We also used best available inputs from the literature, ensured the implemented software and code worked properly through using extreme values and tested the health state transition traces, and compared our results to similar CEA models in the literature.

Results

Clinical Outcomes

In the base-case analysis, LYs were 11.63 in the empirical PP, 11.67 in the universal ticagrelor or prasugrel arm, and 11.59 in the universal clopidogrel arms (Table 2.2). After incorporating the utility values for the different health states, patients had an estimated 9.92, 10.00, and 9.84 QALYs.

Costs and Cost Utility

Lifetime costs per patient averaged $72,402, $73,325, and $72,670 for the empirical PP, universal clopidogrel or prasugrel, and universal clopidogrel arms, respectively (Table 2.2). Estimated drug costs in the 1-year model were lowest for generic clopidogrel ($16) and highest for the branded newer $P2Y_{12}$ inhibitors ($4,662). AE costs were similarly lowest for generic

clopidogrel ($423), followed by PP ($444) and newer $P2Y_{12}$ inhibitor ($503). Treatment with universal prasugrel and ticagrelor compared to current clinical prescribing patterns resulted in $923 lower total costs and 0.08 fewer QALYs, translating into an incremental cost-effectiveness ratio of $11,144 per QALY gained. On the other hand, universal treatment with clopidogrel was dominated as this strategy resulted in higher total costs and lower QALYs.

Sensitivity Analyses

In the one-way sensitivity analysis for empirical PP compared to a universal ticagrelor or prasugrel treatment strategy, the most influential parameters of the ICER were 1-year non-fatal MI rates for both treatment arms, discount rate, and 1-year revascularization rates for both treatment arms (Figure 2.3). At the highest end of 1-year non-fatal MI rate for empirical PP, the resultant ICER was $23,805/QALY. Comparing empirical PP to universal clopidogrel, the most influential parameters in this sensitivity analyses were the same (Figure 2.4).

In the probabilistic sensitivity analysis for empirical PP versus universal ticagrelor or prasugrel, 3.56% of simulations resulted in fewer incremental QALYS and higher incremental costs for PP, while most simulations (96.44%) resulted in fewer incremental costs and QALYs (Figure 2.5). For the simulations examining empirical PP vs. universal clopidogrel, 32.86% resulted in higher incremental costs and QALYs for PP, and 67.14% resulted in lower incremental costs and more QALYs. In the cost effectiveness acceptability curve revealed that PP was most likely a cost-effective strategy from a willingness to pay threshold range of $0 to $12,000 (Figure 2.6). Outside of this range, the universal $P2Y_{12}$ was the most favorable cost-effective option.

In the best case scenario where physicians were able to perfectly predict the antiplatelet agent a patient would benefit most from, the model resulted in estimates of 11.68 LYs and 10.02 QALYs at a total cost of $69,653. As a result, this treatment strategy dominated both treatment arms of universal ticagrelor or prasugrel and universal clopidogrel. The ICER of universal treatment with prasugrel or ticagrelor compared to current targeted prescribing showed a downward trend for the first few years but began showing an upward trend after 2013 (Figure 2.7).

Discussion

Empirical targeted prescribing is a treatment strategy that reflects actual clinical practice and how physicians personalize medications to individual patients with acquired knowledge and experience over time. Our model is the first to incorporate heterogeneity of treatment effects from real-world data to assess the potential cost-effectiveness of alternative interventions with $P2Y_{12}$ inhibitors. We showed that universal treatment with ticagrelor or prasugrel is a cost-effective strategy compared to current prescribing patterns or universal treatment with clopidogrel.

In our model, universal treatment with prasugrel and ticagrelor resulted in a favorable ICER ($11,144/QALY gained) compared to actual prescribing practice. This is below the most common low-end threshold in the US of $50,000/QALY.[1] However, empirical targeted prescribing resulted as a dominant strategy compared to treatment with universal clopidogrel. While the incremental differences in total costs and QALYs were small, the sensitivity analyses demonstrated the model to be robust. In the sensitivity analyses, even at the highest end for the

most influential parameters, the resultant ICER fell below the $50,000 QALY threshold, and most simulations supported the finding of the deterministic results. Even though the intent of our study was not necessarily to assess ticagrelor or prasugrel treatment compared to clopidogrel, our estimates of the LYs, QALYs, and ICER of this comparison were similar to published studies suggesting our model structure and input estimates were valid.[15-17]

The deterministic result and most of the PSA simulations of empirical PP vs. universal $P2Y_{12}$ inhibitor fell in quadrant III because the proportion of prescriptions in the PP arm were largely for clopidogrel. This was likely due to familiarity of the medication for physicians, as well as the lower generic drug costs compared to the newer $P2Y_{12}$ inhibitors. Therefore, the lower effectiveness outcomes of clopidogrel influenced the LYs and subsequent QALYs of the PP arm more than the treatment mix of newer $P2Y_{12}$ inhibitors. Since the current guidelines for this population of patients advocate the use of ticagrelor, a newer $P2Y_{12}$ inhibitor, from a policy perspective, this comparison could be thought of as the potential cost-effectiveness of actual clinical practice against absolute adherence to treatment guidelines.[33]

On the other hand, the universal prescription of clopidogrel for this patient population could be interpreted as taking a health plan perspective, in which the use of clopidogrel is advocated through formulary tier restrictions and use of newer $P2Y_{12}$ inhibitors are limited. In this case, actual clinical practice through PP is a dominant strategy as physicians are more effective and cost saving than simply giving all patients clopidogrel.

In the scenario analysis where patients were matched to their optimal medication in terms of effectiveness and safety, this was not surprisingly a dominant strategy, even when factoring in the cost of the pharmacogenetic test. Since patients transition to different health plans on average every 2 to 3 years, payers may be wary of investing in up-front costs when they may not reap the downstream health and economic benefits of their enrollees.[34] However, if similar results held in a different population where the payer could obtain the benefits, such as Medicare or in single payer countries, the return on investment could potentially be a cost-effective or even cost-savings strategy over the patient's lifetime.

There are limitations in this study. Due to the nature of Markov models, patients transitioned between health states in a memory-less way, meaning a patient who cycles through the non-fatal MI and stroke health states multiple times will have the same transition probabilities, utilities, and costs as another patient who may experience only one event. Furthermore, some of the clinical and transition estimates were taken from European countries such as the increased risk of death through hazard ratios, but to lessen concerns, these estimates were taken from a CEA study conducted alongside the pivotal trial for ticagrelor. In addition, whether genetic testing for clopidogrel efficacy improves outcomes is a subject of debate and is not part of clinical guidelines at present but will be clarified with upcoming trials. Finally, the model results are driven primarily by the first year in the model where different outcome probabilities are informed by Aim 1.

In conclusion, passive personalization by physicians, who personalize treatments based on their experience and acquired knowledge, are likely to be cost-effective for either ticagrelor or

prasugrel as compared to universal treatment with clopidogrel alone. Further, universal use of any one antiplatelet was inferior to passive personalization by physicians. Sensitivity analyses supported these results indicating a robust model. These data support robust physician education as well as personalized medical approach to patients in order to improve patient outcomes at less cost.

Tables and Figures

Table 2.1. Key inputs for the two-part cost effectiveness model

	Point estimate	Low	High	Distribution	Source
Passive personalization arm, % prescribed					
Clopidogrel	0.63	0.57	0.70	Normal	Suh et al.
Prasugrel	0.29	0.26	0.31	Normal	Suh et al.
Ticagrelor	0.08	0.07	0.09	Normal	Suh et al.
Transition probabilities					
1-year revascularization, passive personalization	14.92%	13.42%	16.41%	Normal	Suh et al.
1-year non-fatal MI, passive personalization	6.14%	5.52%	6.75%	Normal	Suh et al.
1-year non-fatal stroke, passive personalization	1.63%	1.46%	1.79%	Normal	Suh et al.
1-year revascularization, universal newer $P2Y_{12}$	14.25%	12.82%	15.67%	Normal	Suh et al.
1-year non-fatal MI, universal newer $P2Y_{12}$	4.28%	3.85%	4.71%	Normal	Suh et al.
1-year non-fatal stroke, universal newer $P2Y_{12}$	1.14%	1.03%	1.26%	Normal	Suh et al.
1-year revascularization, universal clopidogrel	15.64%	14.08%	17.20%	Normal	Suh et al.
1-year non-fatal MI, universal clopidogrel	7.89%	7.10%	8.68%	Normal	Suh et al.
1-year non-fatal stroke, universal clopidogrel	2.07%	1.86%	2.27%	Normal	Suh et al.
1-year fatal MI and fatal stroke	7.55%	6.80%	8.31%	Normal	Donahoe et al.
Increased risk of death in the no event state	2.00	1.80	2.20	Log normal	Nikolic et al.
No event/post revascularization to MI	1.90%	1.71%	2.09%	Normal	Nikolic et al.
No event/post revascularization to stroke	0.30%	0.27%	0.33%	Normal	Nikolic et al.
Increased risk of death in the non-fatal MI state	6.00	5.40	6.60	Log normal	Nikolic et al.
Increased risk of death in the post-MI state	3.00	2.70	3.30	Log normal	Nikolic et al.
Post non-fatal MI to stroke	2.00%	1.80%	2.20%	Normal	Hachet et al.
Increased risk of death in the non-fatal stroke state	7.43	6.69	8.17	Log normal	Nikolic et al.
Increased risk of death in the post-stroke state	3.00	2.70	3.30	Log normal	Nikolic et al.

Post non-fatal stroke to MI	1.00%	0.90%	1.10%	Normal	Edwards et al.
Healthcare costs					
1-year no event	$16,720	$15,048	$18,392	Normal	Suh et al.
1-year revascularization	$48,242	$43,418	$53,066	Normal	Suh et al.
1-year non-fatal MI	$54,848	$49,363	$60,333	Normal	Suh et al.
1-year non-fatal stroke	$72,745	$65,471	$80,020	Normal	Suh et al.
No event/post-revascularization	$2,226	$2,003	$2,448	Normal	Nikolic et al.
Non-fatal MI	$25,150	$22,635	$27,665	Normal	Afana et al.
Post-MI	$12,666	$11,399	$13,932	Normal	Nicholson et al.
Non-fatal stroke	$17,314	$15,583	$19,046	Normal	Earnshaw et al.
Post-stroke	$6,533	$5,879	$7,186	Normal	Earnshaw et al.
Genetic test P2Y12	$295	$265	$324	Normal	CPT code 81225
Drug costs					
Clopidogrel, cost per 75 mg tablet	$0.05	$0.04	$0.05	Normal	Federal Supply Schedule
Prasugrel, cost per 10 mg tablet	$15.22	$13.70	$16.75	Normal	Federal Supply Schedule
Ticagrelor, cost per 90 mg tablet	$4.52	$4.07	$4.97	Normal	Federal Supply Schedule
Adverse event costs					
Major bleeding	$10,228	$9,206	$11,251	Normal	DRG 064 & 377
Minor bleeding	$4,436	$3,992	$4,880	Normal	DRG 066 & 379
Quality-of-life (utility) estimate					
No event/post revascularization state	0.90	0.81	0.99	Beta	Cowper et al.
Non-fatal MI and post-MI state	0.70	0.63	0.77	Beta	Sullivan & Ghushchyan
Non-fatal stroke and post-stroke state	0.65	0.59	0.72	Beta	Sullivan & Ghushchyan
Annual QALY decrement, non-fatal MI state	0.04	0.04	0.04	Beta	Sullivan & Ghushchyan

Annual QALY decrement, non-fatal stroke state	0.05	0.05	0.06	Beta	Sullivan & Ghushchyan

CPT current procedural terminology, *DRG* diagnosis related group, *MI* myocardial infarction, *mg* milligram

Table 2.2. Results of the cost effectiveness analysis

	Health state costs	Drug costs	AE costs	Total costs	LYs	QALYs	ICER (QALY)
Current targeted prescribing	$70,242	$1,716	$444	$72,402	11.63	9.92	
Universal treatment with clopidogrel	$72,230	$16	$423	$72,670	11.59	9.84	Dominated
Universal treatment with ticagrelor and prasugrel	$68,160	$4,662	$503	$73,325	11.67	10.00	$11,144.06

AE adverse event, *ICER* incremental cost-effectiveness ratio, *LY*s life-years, *QALY*s quality-adjusted life-years

Figure 2.1. 1-year decision tree

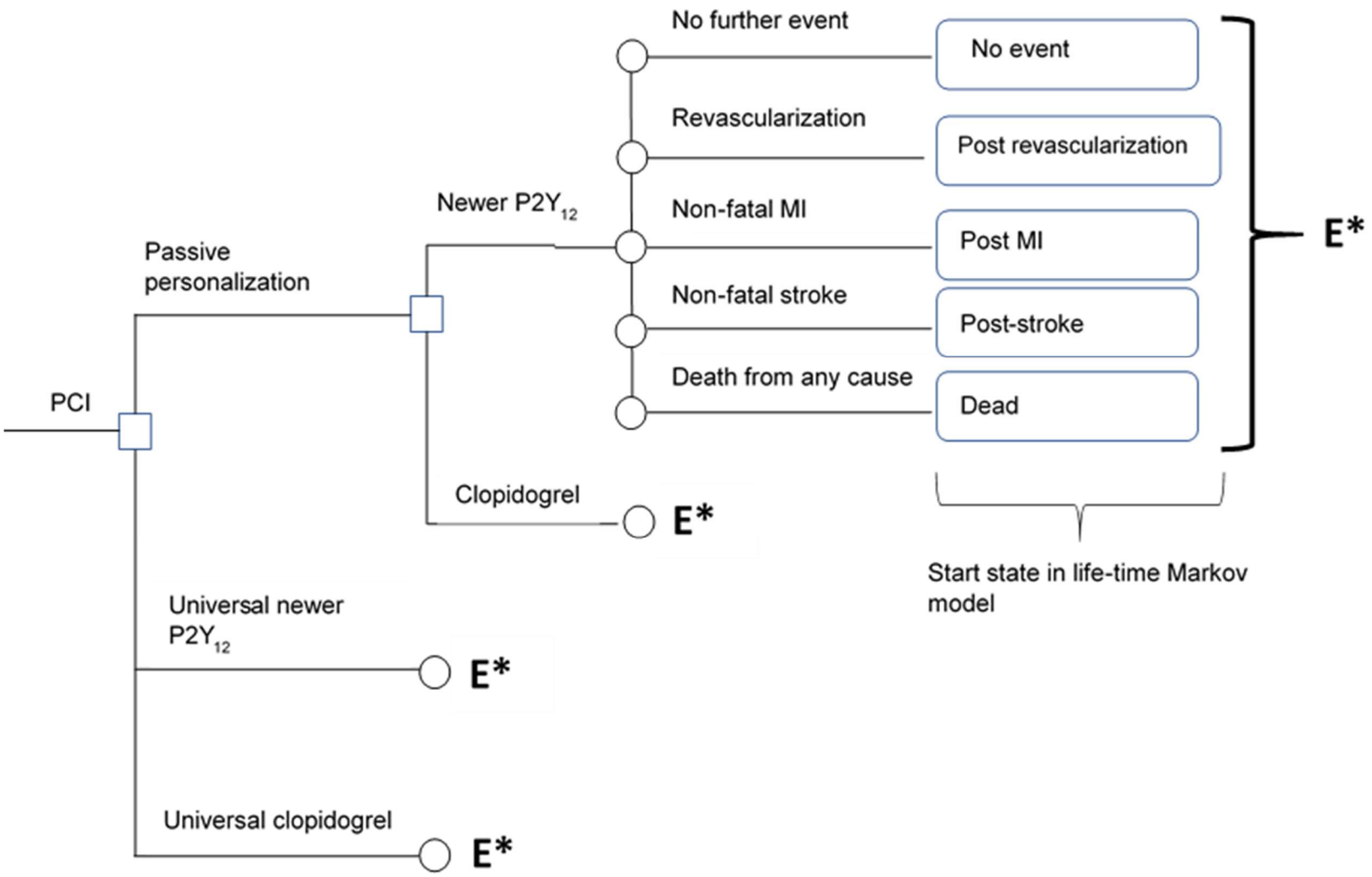


Figure 2.2. Lifetime Markov model

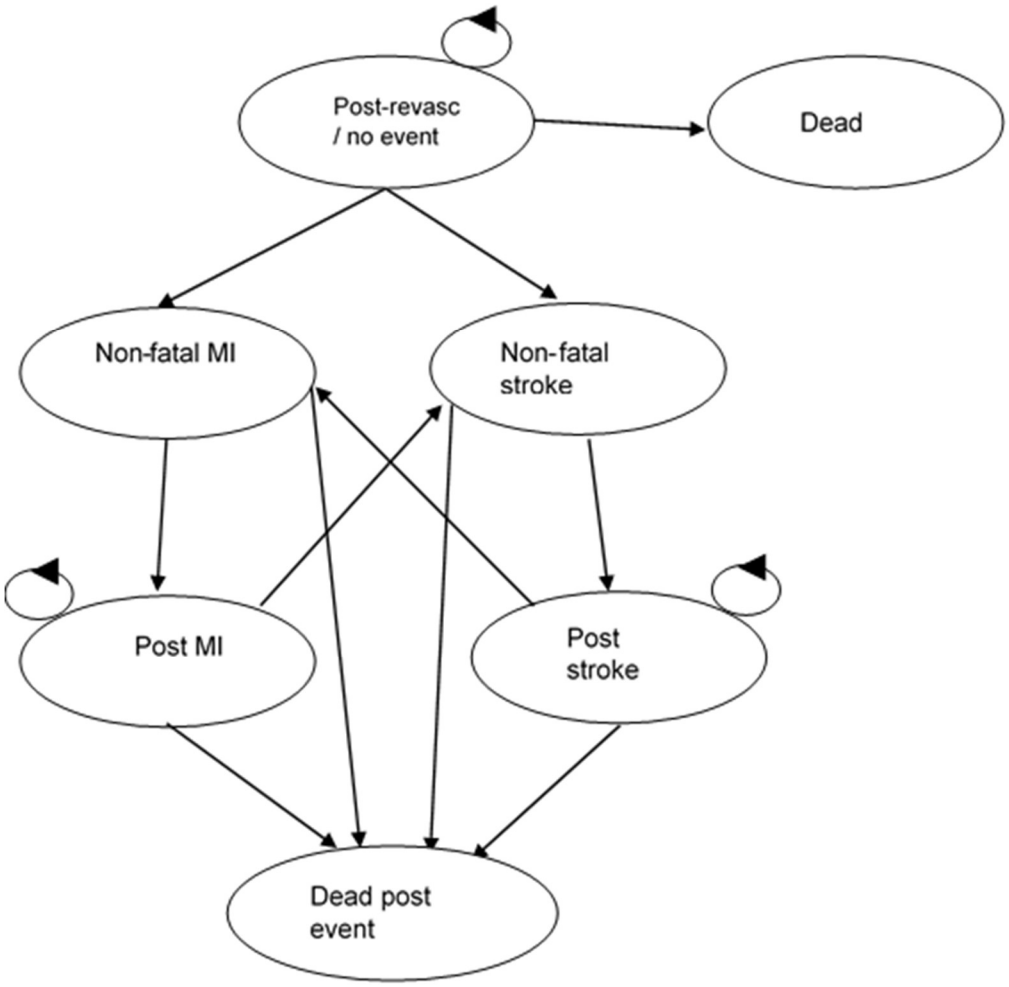


Figure 2.3. Tornado diagram of the one-way sensitivity analysis of passive personalization vs. universal newer P2Y$_{12}$ inhibitor

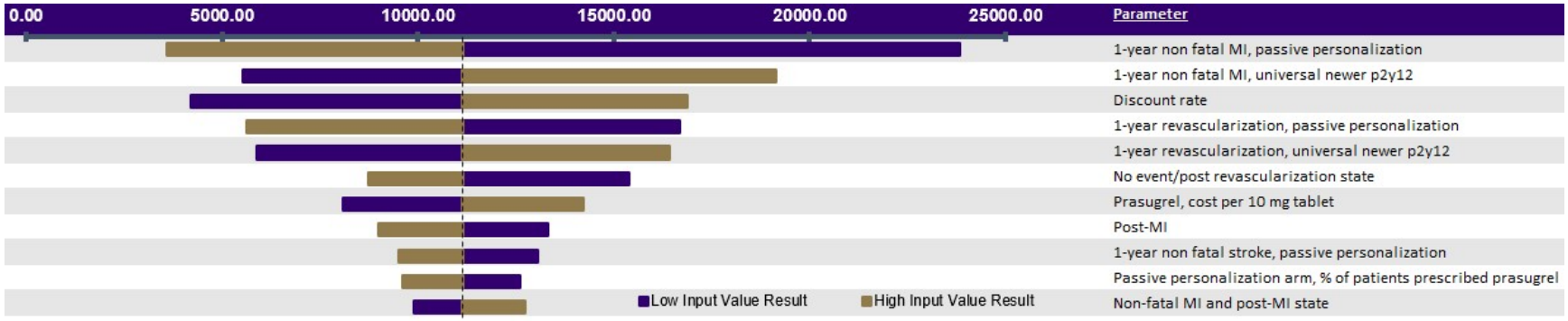


Figure 2.4. Tornado diagram of the one-way sensitivity analysis of passive personalization vs. clopidogrel

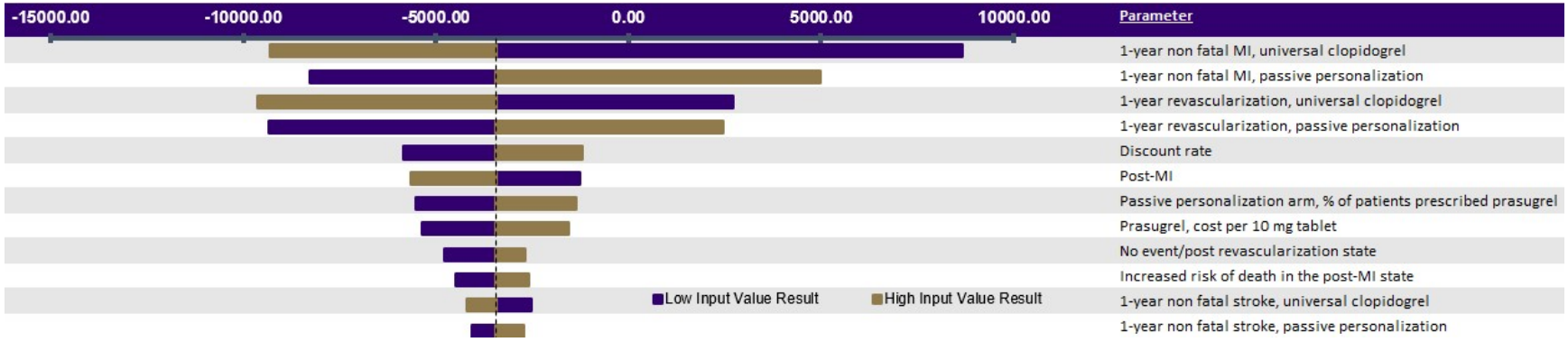


Figure 2.5. Probabilistic sensitivity analysis on incremental cost-effectiveness plane

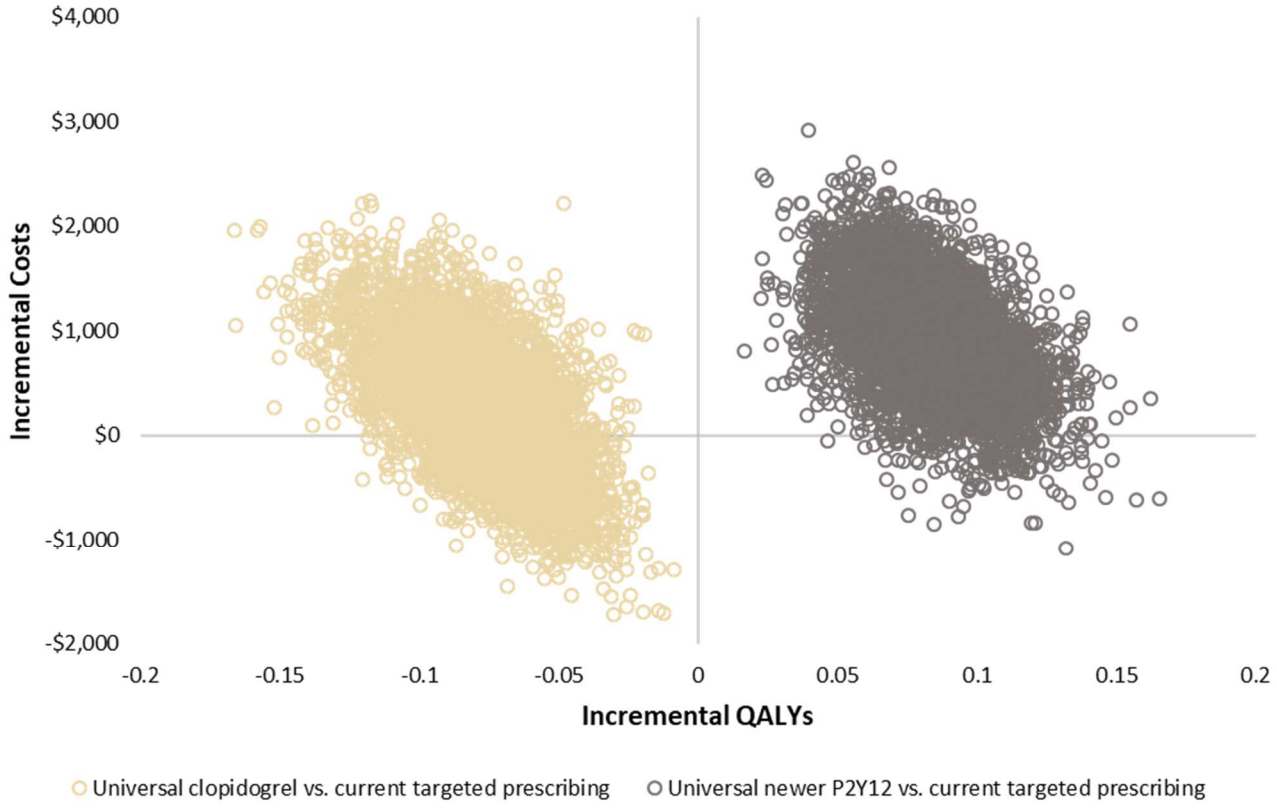


Figure 2.6. Cost effectiveness acceptability curve at different thresholds for willingness to pay

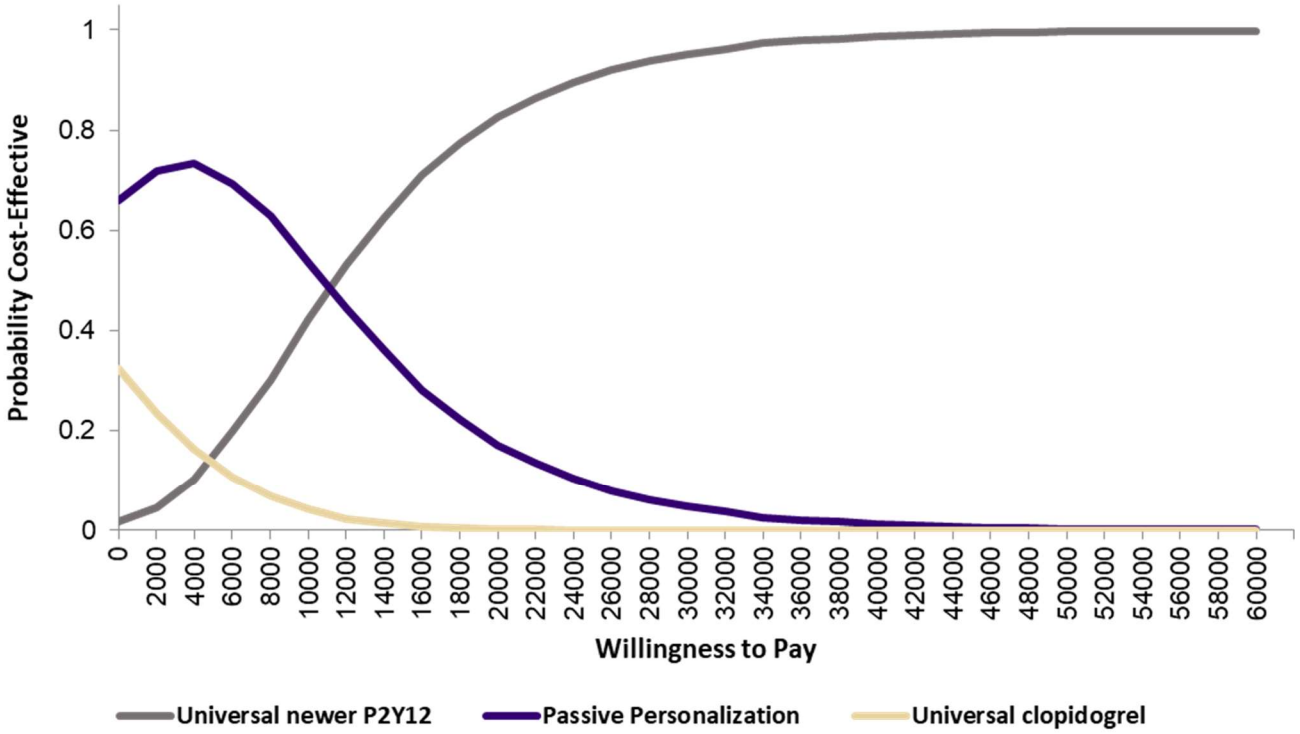
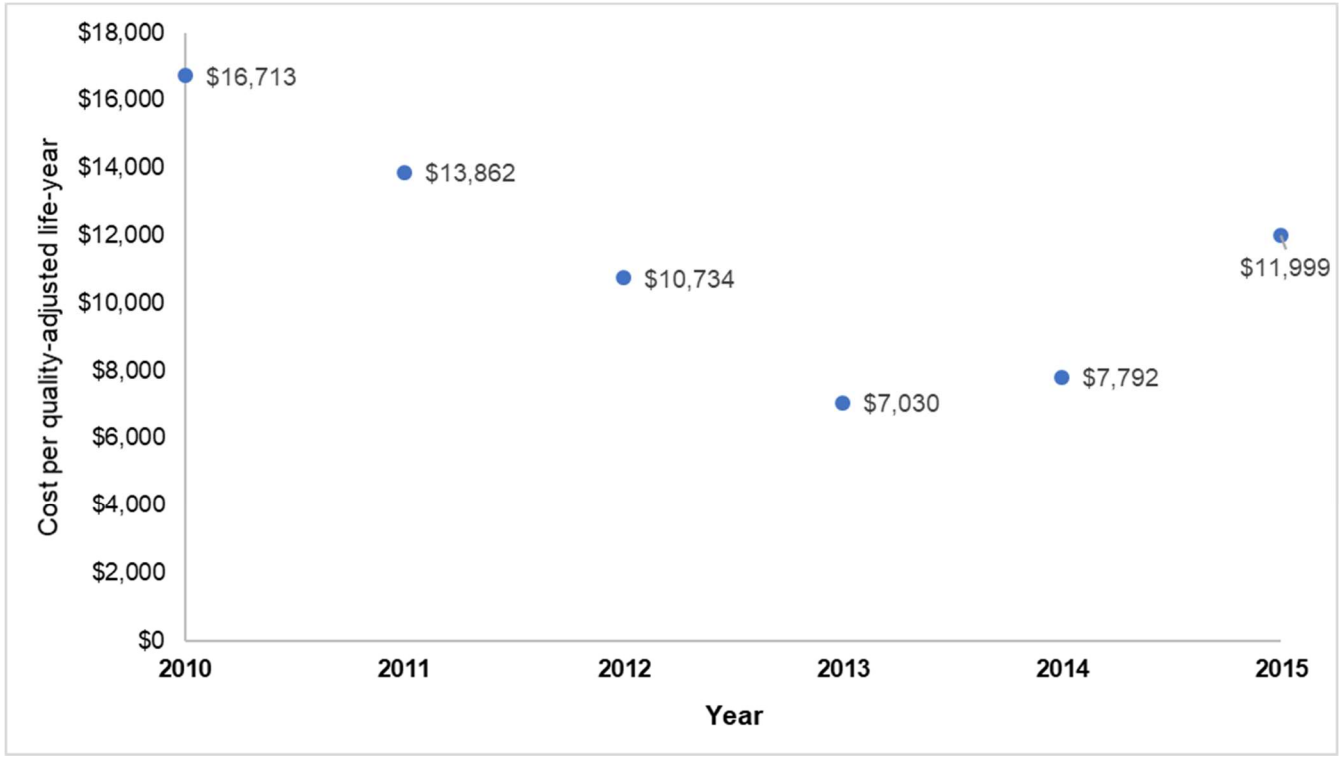


Figure 2.7. Incremental cost-effectiveness ratio of universal treatment with prasugrel or ticagrelor versus empirical targeted prescribing over time



References

1. Neumann P, Cohen J, Weinstein M. Updating cost-effectiveness - the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med.* 2014;371:796-797.
2. Garrison L. Cost-effectiveness and clinical practice guidelines: have we reached a tipping point? - an overview. *Value in Health.* 2016;19:512-515.
3. Espinoza MA, Manca A, Claxton K, Sculpher MJ. The value of heterogeneity for cost-effectiveness subgroup analysis: conceptual framework and application. *Med Decis Making.* 2014;34(8):951-964.
4. Lavelle T, Kent D, Lundquist C, et al. Patient variability seldom assessed in cost-effectiveness studies. *Med Decis Making.* 2018;38(4):487-494.
5. Sculpher M. Subgroups and heterogeneity in cost-effectiveness analysis. *Pharmacoeconomics.* 2008;26(9):799-806.
6. Steinhubl S, Berger P, Mann JI, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA.* 2002;288:2411-2420.
7. Gurbel P, Bliden K, Hiatt B, O'Connor C. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation.* 2003;107(23):2908-2913.
8. Zhang L, Lu J, Dong W, et al. Meta-analysis of comparison of the newer P2Y12 inhibitors (oral preparation or intravenous) to clopidogrel in patients with acute coronary syndrome. *J Cardiovasc Pharmacol.* 2017;69:147-155.
9. Wijeyeratne Y, Heptinstall S. Anti-platelet therapy: ADP receptor antagonists. *Br J of Clin Pharmacol.* 2011;72(4):647-657.
10. Wallentin L, Becker R, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045-1057.
11. Wiviott S, Braunwald E, McCabe C, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001-2015.
12. Basu A, Jena A, Goldman D, Philipson T, Dubois R. Heterogeneity in action: the role of passive personalization in comparative effectiveness research. *Health Econ.* 2014;23(3):359-373.
13. Suh K, Branch K, Carlson J, Basu A. Addressing heterogeneity of treatment effects and passive personalization of P2Y12 inhibitors using a novel instrumental variable method. *TBD.* 2019:TBD.
14. Cowper P, Pan W, Anstrom K, et al. Economic analysis of ticagrelor therapy from a U.S. perspective. *J Am Coll Cardiol.* 2015;65:465-476.
15. Grima D, Brown S, Kamboj L, et al. Cost-effectiveness of ticagrelor versus clopidogrel in patients with acute coronary syndromes in Canada. *Clinicoecon Outcomes Res.* 2014;6:49-62.
16. Mahoney E, Wang K, Arnold S, et al. Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with Prasugrel-Thrombolysis in Myocardial Infarction TRITON-TIMI 38. *Circulation.* 2010;121(1):71-79.

17. Nikolic E, Janzon M, Hauch O, Wallentin L, Henriksson M. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. *Eur Heart J.* 2013;34(3):220-228.
18. Yamwong S, Permsuwan U, Tinmanee S, Sritara P. Long-term cost effectiveness of ticagrelor in patients with acute coronary syndrome in Thailand. *Health Economics Review.* 2014;4:17.
19. Zhao Y, Khoo A, Lin L, et al. Cost-effectiveness analysis of ticagrelor and prasugrel for the treatment of acute coronary syndrome. *Value Health Reg Issues.* 2016;9:22-27.
20. Crespin DJ, Federspiel JJ, Biddle AK, Jonas DE, Rossi JS. Ticagrelor versus genotype-driven antiplatelet therapy for secondary prevention after acute coronary syndrome: a cost-effectiveness analysis. *Value Health.* 2011;14(4):483-491.
21. Li Q, Ganguly R, Ganz M, Gamble C, Dang-Tan T. Real-world clinical effectiveness and cost savings of liraglutide versus sitagliptin in treating type 2 diabetes for 1 and 2 years. *Diabetes Ther.* 2018;9:1279-1293.
22. McQueen RB, Nair KV, Vollmer TL, Campbell J. Incorporating real-world clinical practice in multiple sclerosis economic evaluations. *Expert Rev Pharmacoecon Outcomes Res.* 2015;15:869-872.
23. Donahoe S, Stewart G, McCabe C, et al. Diabetes and mortality following acute coronary syndromes. *JAMA.* 2007;298:765-775.
24. Hachet O, Guenancia C, Stamboul K, et al. Frequency and predictors of stroke after acute myocardial infarction. *Stroke.* 2014:3514-3520.
25. Edwards J, Kapral M, Fang J, Swartz R. Long-term morbidity and mortality in patients without early complications after stroke or transient ischemic attack. *CMAJ.* 2017;189:E954-961.
26. Brilinta [package insert]. AstraZeneca Pharmaceuticals LP, Wilmington, DE; 2019.
27. Effient [package insert]. Eli Lilly and Company, Indianapolis, IN; 2019.
28. Sullivan P, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making.* 2006;26:410-420.
29. Neumann P, Sanders G, Russell L, Siegel J, Ganiats T, eds. *Cost-effectiveness in health and medicine.* 2nd ed. New York: Oxford University Press; 2017.
30. US Department of Veterans Affairs. VA Federal Supply Schedule service. 2019; https://www.fss.va.gov/. Accessed 03/08/2019.
31. Briggs AH, Claxton K, Schulpher MJ. *Decision modelling for health economic evaluation.* Oxford: Oxford University Press; 2006.
32. Vemer P, Corro Ramos I, van Voorn G, Al M, Feenstra T. AdViSHE: a validation-assessment tool of health-economic models for decision makers and model users. *Pharmacoeconomics.* 2016;34(4):349-361.
33. Levine G, Bates E, Bittl J, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation.* 2016;134(10):e123-155.
34. Yeung K, Suh KG, LP, Carlson J. Defining and managing high-priced cures: healthcare payers' opinions. *Value in Health.* 2018;(accepted for publication).

Chapter 3: Exploring heterogeneity of effects across the distribution of medication adherence with $P2Y_{12}$ inhibitors using conditional and unconditional quantile regression approaches

Abstract

Background: Previous research assessing medication adherence with $P2Y_{12}$ inhibitors have shown relatively good adherence rates ranging from 78%-92%. The studies that used administrative claims data to measure adherence defined adherence using an arbitrary cut point of ≥80% medication possession ratio (MPR) or proportion of days covered (PDC). While this method is used frequently, it does not allow the researcher to observe how each factor impacts adherence along the entire distribution. The objective of the study was to use conditional quantile regression (CQR) and unconditional quantile regression (UQR) to assess heterogenous effects of adherence of $P2Y_{12}$ inhibitors and covariates of interest and compare these results to those from a traditional logistic regression framework.

Methods and Results: This study used the commercial claims and encounters databases from IBM® MarketScan® in this study from 2010-2017. We included patients who had an incident percutaneous coronary intervention, used a drug-eluting stent, and filled an incident prescription for a $P2Y_{12}$ inhibitor. Their adherence was measured for 185 days using PDC. Adherence to branded clopidogrel, generic clopidogrel, branded prasugrel, and branded ticagrelor were assessed, along with factors that could impact adherence using logistic regression, CQR, and UQR. In CQR, the effect of a covariate on a quantile of adherence is conditioned on the average values of the other covariates, which limits the interpretability of results. Recent advancements in UQR overcomes this limitation. We found that while adherence to the antiplatelets was

generally good, prasugrel and ticagrelor had significantly lower PDC compared to branded clopidogrel, especially around the 30th percentile where adherence is ~80%. Other covariates such as comorbid depression and living in the southern region affected adherence the most.

Conclusions: Using CQR and UQR allowed for heterogenous assessment of covariates along the adherence distribution, which is not possible with the traditional logistic regression method. Patients who have good, but not excellence adherence, seem to be impacted the most by the newer $P2Y_{12}$ inhibitors.

Background

P2Y12 inhibitors are antiplatelet medications that are recommended in conjunction with aspirin as part of dual antiplatelet therapy (DAPT) for patients who undergo percutaneous coronary intervention (PCI) with drug-eluting stents (DES).[1-3] While previous versions of the guideline have advocated for the use of DAPT for at least one year, the most recent guidelines regarding DAPT after DES recommend a minimum duration of therapy for at least 6 months.[1] These oral medications provide clinical benefits to the patients by lowering their risk of secondary major adverse cardiac events (MACE).[4-7] However, as with any therapy, the patient must adhere to the medications to receive the benefits.

Previous adherence studies have been conducted in this patient setting looking at clopidogrel at its branded stage and as a generic, as well as the two more recently approved branded $P2Y_{12}$ inhibitors, prasugrel and ticagrelor. These medications have shown to have high adherence rates ranging from 78% - 92% with varying follow up times from 1 month to 1 year.[8-15] However,

ticagrelor had lower rates of adherence due to its adverse event of dyspnea or coughing.[13,14] These studies used two methods to measure adherence. One was through surveying the patients, and the other method was through calculating medication possession ratio (MPR) or proportion of days covered (PDC) using administrative claims data. In the latter case, adherence was operationalized as having an MPR or PDC of 80.0% or greater.

There a few limitations with this operational definition of adherence. The first is that the 80.0% cut-off has no fundamental reasoning as to why it should be used to define adherence from a clinical perspective. Another issue arises from using such a strict cut-off to aggregate patients into two arbitrary groups. As a result, while it is more than likely that patients who have a PDC of 80.5% and 79.5% are similar, these patients would be considered different, and the resultant analysis could make spurious associations affecting adherence.

Recent advances in quantile regression (QR) addresses some of these concerns by examining how covariates affect the outcome along its distribution.[16,17] In this way, the entire distribution of adherence could be measured and studied instead of having two rigid groups. The objective of our study was to assess medication adherence to $P2Y_{12}$ inhibitors in patients with acute coronary syndrome for the first six months after undergoing PCI with DES, and to contrast the results with traditional adherence analysis through logistic regression models with two arbitrary groups of adherent and non-adherent.

Methods

Data Source

We used the commercial claims and encounters databases from IBM® MarketScan® in this study from 2010-2017. MarketScan® is composed of fully adjudicated medical (inpatient and outpatient) and pharmaceutical claims. In any given year, there are more than 20 million patients in the database and reflect real-world treatment patterns. As MarketScan® is a deidentified database, the University of Washington Institutional Review Board approved a waiver for the study.

Study population

The study population consisted of patients greater than 18 years of age who underwent an incident PCI with DES starting from 2010; patients who had a PCI event anytime one-year prior were excluded. Patients were then required to have a claim for an incident P2Y12 inhibitor prescription fill 90 days pre- through 30 days post-DES, as used previously.[18] Patients were also required to have continuous enrollment one-year pre- and six months post-DES event to collect baseline variables and outcomes, respectively. Patients were categorized into four groups based on the antiplatelet they initiated and finished for the six-month follow-up period: clopidogrel (brand), clopidogrel (generic), prasugrel, and ticagrelor.

Outcomes and baseline characteristics

The primary outcome that was measured to determine adherence was PDC, which is supported by the Pharmacy Quality Alliance and the Centers for Medicare and Medicaid Services.[19] Rather than simply summing days of supply as in MPR, PDC adjusts by measuring the number of days

"covered" by a prescription. For the logistic models assessing adherence, patients with a PDC value of 80% or greater were considered adherent. In both analyses, baseline characteristics that were adjusted for included age, gender, insurance type, Charlson Comorbidity Index, Elixhauser comorbidities, baseline healthcare utilization, region, and year fixed effects to control for clinical practice time trends.

Statistical analysis

We used conditional quantile regression (CQR) and unconditional quantile regression (UQR) as our primary statistical method to assess adherence. Using quantile regression (QR) allows the analyst to identify different relationships at different parts of the distribution of the dependent variable.[20] As a result, QR allows different slopes of the regression to vary across quantiles of PDC. This contrasts with methods that assess mean levels such as ordinary least squares regression where the association between a covariate and PDC (i.e. the slope) would remain parallel, or the same, at different levels of the quantile. This would mean, for example, that number of unique medications affect people at the 40th percentile of adherence the same way as those at the 10th percentile. While possible, this uniformity in association is not likely.

CQR is a maximum-likelihood procedure that produces regression coefficients that are associated with different quantiles of the conditional distribution of the dependent variable.[21] This results in a coefficient $\hat{\beta}^{\tau}$ that can be interpreted as the marginal effect of a covariate on the τ^{th} quantile of the dependent variable's distribution, conditioned on the mean value of all the other covariates in the model. Because the coefficient is conditioned on the mean value of other

covariates, the interpretation of the coefficient changes when different sets of covariates are included in the model. To obtain coefficients that correspond to effects at the τ^{th} quantile of the dependent variable's distribution, independent of the other covariates in the model, unconditional QR (UQR) was developed.[16] The applicability of this approach has been applied to medication adherence to highlight heterogenous associations previously.[17] To explore differential associations by relevant subpopulations, we also decided to conduct the logistic, CQR, and UQR models in subgroup analyses by gender and age.

Results

The final sample in our study consisted of 35,762 patients. The mean age was similarly around 55 years of age for patients in all four cohorts, and the majority (76.71%) of patients were males (Table 3.1). Approximately 85% of patients had a fee-for-service insurance type, and the remaining patients had a managed care plan. Across the four cohorts, patients were on 6 or 7 unique medications in the baseline period before initiating a $P2Y_{12}$ inhibitor.

The average PDC was 88.74, 90.52, 88.95, and 89.60 for clopidogrel (brand), clopidogrel (generic), prasugrel, and ticagrelor users, respectively (Table 3.2). In all four cohorts, the unconditional PDC was left skewed, with a peak at 100 (Figure 3.1). Approximately 31%, 38%, 29%, and 31% of patients had perfect adherence at the end of the 6 months for clopidogrel (brand), clopidogrel (generic), prasugrel, and ticagrelor users, respectively.

In the logistic regression model, where adherence was defined as ≥80% PDC, patients on branded prasugrel and ticagrelor were significantly less likely to be adherent (odds ratio

(OR)=0.88, 95% confidence interval (CI): (0.80,0.97), OR=0.80, 95% CI: (0.70, 0.92), respectively) compared to branded clopidogrel (Table 3.3). The marginal (unconditional) effect resulted in the probability of adherence declining by 1.54% and 2.76% for prasugrel and ticagrelor, respectively. Adherence for generic clopidogrel did not result in an adherence difference compared to branded clopidogrel. Other associations that resulted in the largest marginal effects of adherence were for taking 8 or more unique medications at baseline (3.07%, 95% CI: (1.92%, 4.21%), the southern region (-3.21%, 95% CI: (-4.28%, -2.13%)), depression (-2.65%, 95% CI: (-3.94%, -1.35%)).

In both the CQR and UQR frameworks, an 80% PDC was around the 30th percentile as shown by the constant (intercept) term (Tables 3.4 and 3.5). In the CQR and UQR models at the 30th percentile, adherence for prasugrel and ticagrelor were highly impacted with both models showing a decrease in adherence compared to branded clopidogrel. The CQR model resulted in the largest negative effects for adherence for the newer $P2Y_{12}$ inhibitors at the 20th quantile. However, these results were much less pronounced in the UQR model, possibly indicating that adherence was not greatly impacted at the lower quantiles. For patients taking 8 or more medications at baseline, having depression, or living in the southern region, the CQR framework resulted in the lowest quantile having the largest negative impact on adherence with monotonically waning effects at each higher quantile. As seen with the newer $P2Y_{12}$ inhibitors in the UQR model, the effects for all three previously mentioned factors were relatively small except for at the 30th percentile.

Subgroup by gender

In the logistic regression model for males, similar effects were found as in the main model (Table 3.6). While generic clopidogrel did not show a difference in adherence compared to branded clopidogrel, prasugrel and ticagrelor showed lower odds of being adherent at 80% PDC (OR=0.89, 95% CI: (0.80, 1.00), OR=0.81, 95% CI: (0.69, 0.95), respectively). In the CQR model, patients on the newer P2Y12 inhibitors had the largest negative effects on adherence at the 20^{th} and 30^{th} percentile (Table 3.7). However, in the UQR framework, relatively large effects were only seen at the 30^{th} percentile (Table 3.8).

In the logistic regression model for females, generic clopidogrel, prasugrel, and ticagrelor all showed lower ORs that were not significant due to wide CIs (Table 3.9). Similar to the results seen in males, the CQR model showed large negative effects on adherence for the newer P2Y12 inhibitors compared to branded clopidogrel at the 20^{th} and 30^{th} percentile (Table 3.10), while the UQR model showed the largest negative impact of adherence at the 30^{th} percentile for these medications (Table 3.11).

Subgroup by age

In patients ≥55 years of age, the logistic model showed no difference in the three antiplatelets of interest compared to branded clopidogrel (Table 3.12). In the CQR and UR models, the newer P2Y12 inhibitors had similar negative effects on adherence at the 20^{th} and 30^{th} percentiles (Tables 3.13 and 3.14). The CQR model showed that comorbid conditions have a considerable

negative impact on adherence at the lower quantiles, and the UQR results mirrored these findings at the 20th percentile.

In patients <55 years of age, the logistic model (Table 3.15) showed significantly lower odds of being adherent for patients on prasugrel and ticagrelor compared to branded clopidogrel (OR=0.82, 95% CI: (0.71, 0.94) and OR=0.76, 95% CI: (0.62, 0.94), respectively). These translated into the probability of adherence declining by 2.67 and 3.63 percentage points, respectively. While the effects on adherence of the newer P2Y12 inhibitors were similarly large at the 20th and 30th percentiles in the CQR framework (Table 3.16), the 30th percentile in the UQR framework clearly had the largest negative impact on adherence for the newer antiplatelet drugs where the PDC was around 84% (Table 3.17). While many comorbid conditions had a significant impact on adherence in the CQR model as seen in the older subgroup, these effects were reduced or became insignificant in the UQR model.

Discussion

Adherence was generally good in all four cohorts with most patients having a PDC over 80% across the four quantiles, similar to previous studies in the literature. [8-15] However, there were still differences that were revealed from the quantile regressions. Compared to traditional logistic regression for assessing adherence using a cutoff of PDC≥80% for adherence, the CQR and UQR frameworks showed more heterogenous effects of covariates across the different quantiles. As a result, we were able to show through the CQR and UQR results that there is a change in the spread of adherence for each covariate at different levels, which was not possible with the traditional logistic regression model.

Compared to branded clopidogrel, the odds of adherence were lower for prasugrel and ticagrelor in the logistic regression and across all but the lowest quantile in the CQR and UQR regressions. We found similar adherence rates to a study that assessed clopidogrel and prasugrel adherence using the same MarketScan® data.[11,15] Furthermore, the authors found predictors of low adherence to be depression and baseline anticoagulant use, while baseline statin use predicted higher adherence. While we found similar significant effects for depression, its effect on adherence were heterogenous across the quantiles as the lowest quantiles were impacted the most in the CQR while using the UQR framework reduced much of its effects. Our covariates that closely matched baseline anticoagulant and statin use (i.e. anticoagulant indication and hyperlipidemia, respectively) showed effects in the same direction as the study by Nordstrom et al. but were not significant in any of the models.[11]

Interestingly, we found that patients who were taking more than 8 medications at baseline and those taking between 4 and 7 had better adherence than those taking less than 4. The direction of this finding persisted across the logistic, CQR, and UQR frameworks, but with varying magnitudes across quantiles. A previous study assessing adherence in cardiovascular disease also found that those with greater medication burden might necessitate stricter compliance to medical routine and in turn improve adherence.[22] The study also concluded that having to take more medications may indicate greater illness severity and this in turn leads to more attention to adherence.[22] This positive association of higher pill burden and higher adherence has also been seen in other severe and symptomatic disease.[23]

Studies that have assessed discontinuation with ticagrelor show higher nonadherence rates compared to studies that assess the other antiplatelets.[13,14] These studies indicate that the side effect of dyspnea is the main reason. While we were unable to assess side effects, we similar found that ticagrelor had significantly lower PDC percentage points compared to the other antiplatelets across the quantiles, and especially around the 30th percentile where the PDC was around 80%. This was most evident when we conducted subgroup analysis in female patients.

A benefit of using the CQR and UQR frameworks is that health care providers would be able to target specific subgroups of patients. For example, some sort of incentive or encouragement could be developed to help prasugrel and ticagrelor patients around the 30th percentile since it seems this adherence quantile is most negatively impacted by these newer $P2Y_{12}$ inhibitors, meaning those who have good adherence but could do slightly better to achieve great adherence. Similarly, extra attention could be paid attention to those who have certain comorbid conditions in patients with age greater than 55 at lower adherence quantiles as shown in Table S9.

Our study has several limitations. Since adherence was generally high and since we measured PDC for only 185 days, there were not enough ties in the data to measure the covariate impacts across all the quantiles. Also, we were confined to the variables that we were able to obtain from MarketScan®, which does not include side effect or socioeconomic information. There could be generalizability issues as this is a commercial database, and as a result, it is unknown if similar findings would be present in a Medicare population. Lastly, as we included patients with at least one prescription fill, we are not able to address primary nonadherence.

This study also had several strengths. This is the first study to the authors' knowledge to compare brand and generic clopidogrel, prasugrel (brand), and ticagrelor (brand) using an administrative claims database. Our study also revealed how certain variables differentially impact adherence across quantiles in both a CQR and UQR framework. This highlighted heterogenous aspects of adherence that are impacted that were not able to be observed in a traditional logistic regression.

Tables and Figures

Table 3.1. Baseline characteristics

	Clopidogrel, brand (n=8,482)	Clopidogrel, generic (n=11,530)	Prasugrel (n=10,463)	Ticagrelor (n=5,287)
Age, mean (sd)	55.33 (6.57)	55.53 (6.59)	54.58 (6.87)	54.85 (6.77)
Male, n (%)	6505 (76.69)	8584 (74.45)	8276 (79.10)	4066 (76.91)
Northeast, n (%)	1162 (13.70)	2153 (18.67)	1503 (14.37)	949 (17.95)
North Central, n (%)	2463 (29.04)	2748 (23.83)	2467 (23.58)	1300 (24.59)
South, n (%)	3077 (36.28)	4585 (39.77)	4831 (46.17)	2445 (46.25)
West, n (%)	1779 (20.97)	2043 (17.72)	1661 (15.88)	591 (11.18)
Charlson Comorbidity Index, mean (sd)	1.34 (1.69)	2.00 (2.15)	1.50 (1.74)	1.82 (1.88)
Fee-for-service, n (%)	6685 (78.81)	9857 (85.49)	9098 (86.95)	4631 (87.59)
Incident DES inpatient setting, n (%)	6528 (76.96)	7831 (67.92)	7810 (74.64)	4215 (79.72)
Incident DES due to STEMI, n (%)	4463 (52.62)	5869 (50.92)	6374 (60.92)	3217 (60.85)
Incident DES due to NSTEMI, n (%)	3946 (46.52)	5549 (48.13)	3986 (38.10)	2022 (38.25)
Incident DES due to unstable angina, n (%)	73 (0.86)	112 (0.97)	103 (0.98)	48 (0.91)
Baseline outpatient visits, mean (sd)	3.45 (11.32)	4.14 (12.88)	2.93 (9.08)	3.27 (11.10)
Baseline inpatient visits, mean (sd)	0.02 (0.18)	0.03 (0.26)	0.02 (0.20)	0.02 (0.23)
Baseline emergency room visits, mean (sd)	0.08 (0.50)	0.11 (0.62)	0.09 (0.70)	0.09 (0.47)
Baseline number of medications, mean (sd)	6.45 (4.92)	6.86 (5.25)	6.10 (4.82)	6.05 (4.96)
Anticoagulant indication,n (%)	507 (5.98)	1100 (9.54)	532 (5.09)	279 (5.28)
Hyperlipidemia, n(%)	4644 (54.75)	6777 (58.8)	5588 (53.41)	2800 (52.96)
Valvular disease, n (%)	465 (5.48)	929 (8.06)	581 (5.55)	328 (6.20)
Hypertension, n (%)	4748 (55.98)	7485 (64.92)	5995 (57.30)	3034 (57.39)
Chronic pulmonary disease, n (%)	777 (9.16)	1607 (13.94)	1058 (10.11)	591 (11.18)
Diabetes without complications, n (%)	2024 (23.86)	3337 (28.94)	2661 (25.43)	1343 (25.40)
Diabetes with complications, n (%)	538 (6.34)	1064 (9.23)	680 (6.50)	401 (7.59)
Hypothyroidism, n (%)	704 (8.30)	1255 (10.89)	962 (9.19)	566 (10.71)
Obesity, n (%)	1061 (12.51)	2298 (19.93)	1649 (15.76)	1000 (18.91)

Fluid & electrolyte disorders, n (%)	614 (7.24)	1239 (10.75)	732 (7.00)	464 (8.78)
Deficiency anemias, n (%)	559 (6.59)	1163 (10.09)	674 (6.44)	385 (7.28)
Depression, n (%)	537 (6.33)	1132 (9.82)	790 (7.55)	435 (8.23)
Renal disease, n (%)	352 (4.15)	798 (6.92)	406 (3.88)	265 (5.01)
Peripheral artery or vascular disease, n (%)	551 (6.50)	980 (8.50)	608 (5.81)	320 (6.05)

Table 3.2. Unadjusted summary measures of $P2Y_{12}$ inhibitors

	Clopidogrel, brand n=8,477	Clopidogrel, generic n=11,504	Prasugrel n=10,448	Ticagrelor n=5,276
PDC, mean (sd)	88.74 (19.20)	90.52 (17.60)	88.95 (18.01)	89.60 (16.81)
Quantile				
Q10	64.52	64.52	64.52	64.52
Q20	80.65	84.95	80.65	80.65
Q30	93.01	94.62	90.32	90.32
Q40	96.77	96.77	95.70	95.16
Q50	96.77	96.77	96.77	96.77

Table 3.3. Logistic regression for adherence (PDC≥80%)

	Odds ratio	95% CI	Average marginal effect (dy/dx)	95% CI for marginal effects
Clopidogrel, generic (ref: clopidogrel, brand)	0.98	(0.87, 1.11)	-0.21	(-1.62, 1.19)
Prasugrel (ref: clopidogrel, brand)	**0.88**	(0.80, 0.97)	**-1.54**	(-2.69, -0.40)
Ticagrelor (ref: clopidogrel, brand)	**0.80**	(0.70, 0.92)	**-2.76**	(-4.48, -1.03)
Age	**1.02**	(1.02, 1.03)	**0.27**	(0.22, 0.33)
Male	1.07	(1.00, 1.15)	0.83	(-0.06, 1.72)
Charlson Comorbidity Index	**0.95**	(0.93, 0.97)	**-0.63**	(-0.89, -0.36)
Fee-for-service (ref: managed care)	1.07	(0.98, 1.16)	0.82	(-0.24, 1.87)
Incident DES inpatient setting	1.03	(0.96, 1.12)	0.41	(-0.52, 1.35)
Incident DES due to STEMI (ref: unstable angina)	**1.22**	(1.12, 1.34)	**2.49**	(1.39, 3.60)
Incident DES due to NSTEMI (ref: unstable angina)	**1.11**	(1.01, 1.21)	**1.24**	(0.10, 2.38)
Baseline outpatient visits	**0.99**	(0.99, 1.00)	**-0.05**	(-0.08, -0.02)
Baseline inpatient visits	**0.89**	(0.78, 0.99)	**-1.50**	(-2.99, -0.02)
Baseline emergency room visits	0.95	(0.89, 1.00)	-0.67	(-1.38, 0.03)
Baseline unique medications, ≥4 and <8 (ref: <4)	**1.09**	(1.01, 1.18)	**1.15**	(0.11, 2.20)
Baseline unique medications, ≥8 (ref: <4)	**1.28**	(1.17, 1.41)	**3.07**	(1.92, 4.21)
Anticoagulant indication	0.96	(0.85, 1.08)	-0.53	(-1.99, 0.93)
Hyperlipidemia	1.04	(0.97, 1.11)	0.46	(-0.39, 1.31)
Valvular disease	**0.85**	(0.76, 0.96)	**-1.97**	(-3.41, -0.53)
Hypertension	**0.84**	(0.79, 0.90)	**-2.12**	(-2.97, -1.27)
Chronic pulmonary disease	0.98	(0.89, 1.08)	-0.29	(-1.49, 0.90)
Diabetes without complications	**0.84**	(0.78, 0.91)	**-2.11**	(-3.11, -1.12)
Diabetes with complications	0.92	(0.81, 1.04)	-1.08	(-2.61, 0.45)
Hypothyroidism	1.04	(0.94, 1.16)	0.52	(-0.73, 1.78)
Obesity	**1.11**	(1.02, 1.20)	**1.24**	(0.22, 2.25)
Fluid & electrolyte disorders	**0.89**	(0.80, 0.99)	**-1.45**	(-2.75, -0.14)
Deficiency anemias	0.92	(0.82, 1.03)	-1.02	(-2.40, 0.37)

Depression	**0.81**	(0.73, 0.90)	**-2.65**	(-3.94, -1.35)
Renal disease	1.01	(0.87, 1.17)	0.16	(-1.66, 1.99)
Peripheral artery or vascular disease	**0.88**	(0.78, 0.98)	**-1.62**	(-3.03, -0.20)
North Central (ref: Northeast)	1.00	(0.90, 1.10)	-0.03	(-1.16, 1.11)
South (ref: Northeast)	**0.77**	(0.71, 0.85)	**-3.21**	(-4.28, -2.13)
West (ref: Northeast)	1.03	(0.93, 1.16)	0.39	(-0.87, 1.64)

DES, drug eluting stent; PDC, proportion of days covered

Boldfaced estimates indicated statistical significance (p-value ≤ 0.05)

Table 3.4. Conditional quantile regression results for PDC (adherence)

	Q10	Q20	Q30	Q40
Clopidogrel, generic (ref: clopidogrel, brand)	0.61	-0.50	-0.56	0.02
Prasugrel (ref: clopidogrel, brand)	-1.31	**-3.43**	**-2.84**	**-0.81**
Ticagrelor (ref: clopidogrel, brand)	-1.98	**-5.16**	**-4.05**	**-1.58**
Age	**0.48**	**0.34**	**0.21**	**0.07**
Male	0.95	**1.15**	0.55	0.14
Charlson Comorbidity Index	**-1.82**	**-0.79**	**-0.40**	**-0.15**
Fee-for-service (ref: managed care)	1.47	**1.61**	**1.06**	0.08
Incident DES inpatient setting	0.09	0.21	0.29	0.20
Incident DES due to STEMI (ref: unstable angina)	**5.33**	**2.80**	**1.16**	**0.38**
Incident DES due to NSTEMI (ref: unstable angina)	**4.14**	**2.00**	0.60	0.22
Baseline outpatient visits	-0.08	**-0.11**	**-0.07**	**-0.04**
Baseline inpatient visits	-2.53	**-2.55**	**-2.68**	**-2.33**
Baseline emergency room visits	**-2.13**	**-1.72**	**-0.82**	**-0.57**
Baseline unique medications, ≥4 and <8 (ref: <4)	**3.76**	**1.27**	0.70	0.27
Baseline unique medications, ≥8 (ref: <4)	**7.16**	**3.58**	**1.57**	**0.57**
Anticoagulant indication	-2.04	-0.34	-0.09	0.11
Hyperlipidemia	1.78	0.42	0.30	0.12
Valvular disease	**-4.9**	-1.70	**-1.32**	-0.14
Hypertension	**-4.66**	**-1.63**	**-0.81**	-0.25
Chronic pulmonary disease	-2.68	-1.38	-0.95	-0.13
Diabetes without complications	**-2.85**	**-2.91**	**-2.33**	**-0.69**
Diabetes with complications	-3.06	-1.65	**-2.25**	**-1.11**
Hypothyroidism	1.57	0.28	0.29	-0.04
Obesity	2.09	**1.37**	0.65	0.21
Fluid & electrolyte disorders	**-3.62**	**-1.73**	-0.79	-0.40
Deficiency anemias	-1.34	-1.63	-0.99	-0.31
Depression	**-4.71**	**-3.73**	**-2.84**	**-0.95**
Renal disease	1.47	0.57	0.69	0.07
Peripheral artery or vascular disease	-3.12	**-2.41**	**-2.13**	**-0.93**
North Central (ref: Northeast)	0.64	-0.77	-0.24	-0.06
South (ref: Northeast)	**-5.36**	**-4.95**	**-3.13**	**-0.96**
West (ref: Northeast)	1.21	-1.13	-0.18	-0.10
Constant	37.31	65.55	81.20	91.91

DES, drug eluting stent; PDC, proportion of days covered

Boldfaced estimates indicated statistical significance (p-value ≤ 0.05)

Table 3.5. Unconditional quantile regression results for PDC (adherence)

	Q10	Q20	Q30	Q40
Clopidogrel, generic (ref: clopidogrel, brand)	-0.12	-0.14	0.35	0.11
Prasugrel (ref: clopidogrel, brand)	-0.05	**-0.69**	**-2.63**	**-0.61**
Ticagrelor (ref: clopidogrel, brand)	0.00	**-1.05**	**-4.90**	**-1.00**
Age	**0.10**	**0.11**	**0.26**	**0.05**
Male	0.08	**0.33**	**0.73**	0.12
Charlson Comorbidity Index	**-0.37**	**-0.26**	**-0.53**	**-0.10**
Fee-for-service (ref: managed care)	0.13	0.32	**1.41**	0.02
Incident DES inpatient setting	-0.13	0.18	0.19	**0.20**
Incident DES due to STEMI (ref: unstable angina)	**1.64**	**0.93**	**1.51**	**0.27**
Incident DES due to NSTEMI (ref: unstable angina)	**0.78**	**0.52**	**0.88**	**0.16**
Baseline outpatient visits	**-0.02**	**-0.03**	**-0.06**	**-0.01**
Baseline inpatient visits	-0.89	**-0.94**	**-1.94**	**-0.25**
Baseline emergency room visits	**-0.57**	-0.34	-0.67	-0.09
Baseline unique medications, ≥4 and <8 (ref: <4)	**0.62**	**0.44**	**1.02**	**0.17**
Baseline unique medications, ≥8 (ref: <4)	**1.57**	**1.25**	**2.05**	**0.33**
Anticoagulant indication	-0.01	-0.20	-0.02	0.06
Hyperlipidemia	0.44	0.16	0.27	0.07
Valvular disease	**-1.26**	**-0.91**	-1.23	-0.14
Hypertension	**-0.77**	**-0.79**	**-1.33**	**-0.23**
Chronic pulmonary disease	-0.63	-0.12	-0.89	-0.13
Diabetes without complications	**-0.93**	**-0.85**	**-2.45**	**-0.49**
Diabetes with complications	-0.28	-0.52	**-1.67**	-0.09
Hypothyroidism	0.39	0.20	0.18	0.01
Obesity	0.36	**0.50**	**0.88**	0.13
Fluid & electrolyte disorders	**-1.20**	**-0.65**	**-1.18**	**-0.20**
Deficiency anemias	0.15	-0.44	-0.65	-0.09
Depression	**-1.11**	**-1.13**	**-2.59**	**-0.54**
Renal disease	0.29	-0.01	0.84	0.12
Peripheral artery or vascular disease	-0.73	**-0.70**	**-2.62**	**-0.45**
North Central (ref: Northeast)	-0.11	0.01	-0.51	-0.04
South (ref: Northeast)	**-1.07**	**-1.23**	**-3.84**	**-0.62**
West (ref: Northeast)	0.16	0.15	-0.07	0.07
Constant	60.22	76.30	79.40	94.46

DES, drug eluting stent; PDC, proportion of days covered

Boldfaced estimates indicated statistical significance (p-value ≤ 0.05)

Table 3.6. Logistic regression for adherence (PDC≥80%), males

Variables	Odds ratio	95% CI	Average marginal effect (dy/dx)	95% CI for marginal effects
Clopidogrel, generic (ref: clopidogrel, brand)	1.01	(0.88, 1.16)	0.07	(-1.53, 1.68)
Prasugrel (ref: clopidogrel, brand)	**0.89**	(0.80, 1.00)	**-1.37**	(-2.66, -0.07)
Ticagrelor (ref: clopidogrel, brand)	**0.81**	(0.69, 0.95)	**-2.62**	(-4.57, -0.67)
Age	**1.02**	(1.02, 1.03)	**0.26**	(0.20, 0.32)
Charlson Comorbidity Index	**0.94**	(0.92, 0.96)	**-0.75**	(-1.05, -0.44)
Fee-for-service (ref: managed care)	1.08	(0.98, 1.20)	0.98	(-0.20, 2.16)
Incident DES inpatient setting	1.09	(1.00, 1.19)	1.03	(-0.03, 2.08)
Incident DES due to STEMI (ref: unstable angina)	**1.21**	(1.09, 1.34)	**2.33**	(1.08, 3.57)
Incident DES due to NSTEMI (ref: unstable angina)	**1.14**	(1.02, 1.27)	**1.58**	(0.26, 2.90)
Baseline outpatient visits	1.00	(0.99, 1.00)	-0.04	(-0.08, 0.00)
Baseline inpatient visits	**0.85**	(0.74, 0.98)	**-1.97**	(-3.66, -0.28)
Baseline emergency room visits	0.94	(0.88, 1.01)	-0.74	(-1.56, 0.09)
Baseline unique medications, ≥4 and <8 (ref: <4)	1.08	(0.99, 1.18)	0.97	(-0.17, 2.10)
Baseline unique medications, ≥8 (ref: <4)	**1.26**	(1.14, 1.41)	**2.81**	(1.53, 4.09)
Anticoagulant indication	0.91	(0.80, 1.04)	-1.12	(-2.75, 0.51)
Hyperlipidemia	1.04	(0.96, 1.12)	0.46	(-0.50, 1.43)
Valvular disease	**0.81**	(0.71, 0.93)	**-2.51**	(-4.19, -0.82)
Hypertension	**0.84**	(0.77, 0.91)	**-2.16**	(-3.12, -1.20)
Chronic pulmonary disease	0.97	(0.86, 1.10)	-0.32	(-1.77, 1.13)
Diabetes without complications	**0.86**	(0.78, 0.95)	**-1.81**	(-2.95, -0.67)
Diabetes with complications	0.97	(0.84, 1.14)	-0.32	(-2.18, 1.54)
Hypothyroidism	1.05	(0.91, 1.20)	0.56	(-1.10, 2.22)
Obesity	**1.14**	(1.04, 1.26)	**1.63**	(0.42, 2.84)
Fluid & electrolyte disorders	0.89	(0.78, 1.01)	-1.41	(-2.99, 0.16)
Deficiency anemias	0.89	(0.77, 1.03)	-1.40	(-3.11, 0.31)
Depression	**0.81**	(0.71, 0.93)	**-2.51**	(-4.18, -0.84)

Renal disease	0.99	(0.83, 1.18)	-0.14	(-2.24, 1.96)
Peripheral artery or vascular disease	0.91	(0.80, 1.05)	-1.08	(-2.77, 0.60)
North Central (ref: Northeast)	1.00	(0.89, 1.12)	-0.03	(-1.30, 1.24)
South (ref: Northeast)	**0.78**	(0.70, 0.86)	**-3.08**	(-4.29, -1.88)
West (ref: Northeast)	0.99	(0.88, 1.12)	-0.09	(-1.48, 1.31)

Table 3.7. Conditional quantile regression results for PDC (adherence), males

	Q10	Q20	Q30	Q40
Clopidogrel, generic (ref: clopidogrel, brand)	1.03	0.28	-0.43	0.07
Prasugrel (ref: clopidogrel, brand)	-0.88	**-2.88**	**-2.49**	**-0.69**
Ticagrelor (ref: clopidogrel, brand)	-2.23	**-4.72**	**-3.76**	**-1.34**
Age	**0.47**	**0.34**	**0.20**	**0.07**
Charlson Comorbidity Index	**-2.17**	**-0.91**	**-0.42**	**-0.14**
Fee-for-service (ref: managed care)	2.34	**2.09**	**1.02**	0.11
Incident DES inpatient setting	1.47	1.20	0.46	0.31
Incident DES due to STEMI (ref: unstable angina)	**5.09**	**2.35**	1.00	0.28
Incident DES due to NSTEMI (ref: unstable angina)	**4.44**	1.30	0.14	0.04
Baseline outpatient visits	0.00	**-0.07**	**-0.06**	**-0.03**
Baseline inpatient visits	-2.47	**-3.87**	**-3.20**	**-2.44**
Baseline emergency room visits	**-2.81**	**-1.22**	-0.67	**-0.45**
Baseline unique medications, ≥4 and <8 (ref: <4)	**3.10**	1.03	0.58	0.14
Baseline unique medications, ≥8 (ref: <4)	**6.46**	**2.91**	**1.32**	**0.44**
Anticoagulant indication	**-4.62**	-1.64	-0.15	0.05
Hyperlipidemia	1.21	0.99	0.24	0.15
Valvular disease	**-4.75**	**-2.98**	**-2.07**	**-0.56**
Hypertension	**-4.59**	**-2.14**	**-0.79**	-0.22
Chronic pulmonary disease	-2.47	-1.46	-1.20	-0.11
Diabetes without complications	-2.35	**-2.64**	**-2.00**	**-0.46**
Diabetes with complications	0.21	-1.16	-1.42	-0.55
Hypothyroidism	1.13	0.38	0.02	-0.03
Obesity	2.11	**1.93**	0.68	0.19
Fluid & electrolyte disorders	-3.50	-1.07	-0.85	-0.27
Deficiency anemias	-2.81	-2.13	-1.03	-0.25
Depression	**-6.47**	**-4.07**	**-3.36**	**-1.16**
Renal disease	0.77	0.25	-0.08	-0.35
Peripheral artery or vascular disease	-1.97	-1.56	-1.06	**-0.59**
North Central (ref: Northeast)	0.86	-0.92	-0.29	-0.10
South (ref: Northeast)	**-5.43**	**-4.69**	**-2.80**	**-0.82**
West (ref: Northeast)	0.21	-1.40	-0.44	-0.18
Constant	37.97	65.05	81.99	92.45

DES, drug eluting stent; PDC, proportion of days covered

Boldfaced estimates indicated statistical significance (p-value ≤ 0.05)

Table 3.8. Unconditional quantile regression results for PDC (adherence), males

	Q10	Q20	Q30	Q40
Clopidogrel, generic (ref: clopidogrel, brand)	0.00	0.00	0.49	0.17
Prasugrel (ref: clopidogrel, brand)	-0.01	-0.62	**-2.04**	**-0.58**
Ticagrelor (ref: clopidogrel, brand)	-0.05	-1.02	**-4.00**	**-0.98**
Age	**0.10**	0.11	**0.21**	**0.05**
Charlson Comorbidity Index	**-0.38**	-0.32	**-0.47**	**-0.11**
Fee-for-service (ref: managed care)	0.20	0.40	**1.29**	0.04
Incident DES inpatient setting	0.08	0.46	0.59	**0.29**
Incident DES due to STEMI (ref: unstable angina)	**1.46**	0.91	**1.08**	**0.22**
Incident DES due to NSTEMI (ref: unstable angina)	0.77	0.66	0.40	0.04
Baseline outpatient visits	0.00	-0.02	**-0.05**	**-0.01**
Baseline inpatient visits	**-1.88**	-1.32	-1.49	-0.22
Baseline emergency room visits	-0.56	-0.38	-0.50	-0.09
Baseline unique medications, ≥4 and <8 (ref: <4)	0.50	0.38	0.62	0.10
Baseline unique medications, ≥8 (ref: <4)	**1.40**	1.20	**1.35**	**0.28**
Anticoagulant indication	-0.52	-0.50	0.00	0.04
Hyperlipidemia	0.35	0.18	0.37	0.09
Valvular disease	**-1.28**	-1.24	**-2.05**	**-0.33**
Hypertension	**-0.90**	**-0.84**	**-1.22**	**-0.22**
Chronic pulmonary disease	-0.65	-0.15	-0.75	-0.14
Diabetes without complications	**-0.93**	-0.76	**-1.74**	**-0.43**
Diabetes with complications	0.04	-0.21	-0.88	-0.01
Hypothyroidism	0.44	0.22	0.04	0.04
Obesity	0.45	**0.69**	**1.10**	0.13
Fluid & electrolyte disorders	-0.99	-0.62	-0.75	-0.13
Deficiency anemias	-0.01	-0.63	-0.42	-0.07
Depression	**-1.49**	-1.17	**-2.76**	**-0.67**
Renal disease	-0.02	-0.21	-0.03	-0.03
Peripheral artery or vascular disease	-0.40	-0.46	**-1.57**	**-0.34**
North Central (ref: Northeast)	0.01	0.00	-0.58	-0.07
South (ref: Northeast)	**-0.96**	-1.25	**-3.23**	**-0.58**
West (ref: Northeast)	-0.01	-0.05	-0.36	0.00
Constant	60.23	76.45	82.28	94.51

DES, drug eluting stent; PDC, proportion of days covered

Boldfaced estimates indicated statistical significance (p-value ≤ 0.05)

Table 3.9. Logistic regression for adherence (PDC≥80%), females

Variables	Odds ratio	95% CI	Average marginal effect (dy/dx)	95% CI for marginal effects
Clopidogrel, generic (ref: clopidogrel, brand)	0.91	(0.71, 1.15)	-1.23	(-4.17, 1.71)
Prasugrel (ref: clopidogrel, brand)	0.84	(0.69, 1.02)	-2.17	(-4.59, 0.25)
Ticagrelor (ref: clopidogrel, brand)	0.77	(0.59, 1.02)	-3.35	(-6.99, 0.29)
Age	**1.02**	(1.02, 1.03)	**0.32**	(0.20, 0.43)
Charlson Comorbidity Index	0.98	(0.94, 1.02)	-0.30	(-0.82, 0.22)
Fee-for-service (ref: managed care)	1.03	(0.86, 1.23)	0.41	(-1.89, 2.71)
Incident DES inpatient setting	0.88	(0.75, 1.03)	-1.64	(-3.66, 0.38)
Incident DES due to STEMI (ref: unstable angina)	**1.25**	(1.04, 1.51)	**2.92**	(0.52, 5.32)
Incident DES due to NSTEMI (ref: unstable angina)	1.03	(0.86, 1.23)	0.35	(-1.94, 2.63)
Baseline outpatient visits	**0.99**	(0.99, 1.00)	**-0.08**	(-0.13, -0.03)
Baseline inpatient visits	0.98	(0.76, 1.25)	-0.32	(-3.54, 2.91)
Baseline emergency room visits	0.95	(0.87, 1.05)	-0.64	(-1.87, 0.59)
Baseline unique medications, ≥4 and <8 (ref: <4)	1.18	(0.98, 1.42)	2.36	(-0.26, 4.98)
Baseline unique medications, ≥8 (ref: <4)	**1.38**	(1.14, 1.66)	**4.30**	(1.67, 6.93)
Anticoagulant indication	1.16	(0.90, 1.05)	1.96	(-1.34, 5.27)
Hyperlipidemia	1.04	(0.90, 1.19)	0.46	(-1.36, 2.28)
Valvular disease	0.94	(0.76, 1.16)	-0.80	(-3.56, 1.95)
Hypertension	**0.86**	(0.74, 0.99)	**-1.97**	(-3.83, -0.11)
Chronic pulmonary disease	0.97	(0.82, 1.15)	-0.35	(-2.51, 1.80)
Diabetes without complications	**0.80**	(0.68, 0.93)	**-2.97**	(-5.01, -0.92)
Diabetes with complications	**0.80**	(0.65, 1.00)	**-2.82**	(-5.61, -0.03)
Hypothyroidism	1.03	(0.88, 1.20)	0.32	(-1.67, 2.31)
Obesity	1.02	(0.88, 1.19)	0.29	(-1.65, 2.22)
Fluid & electrolyte disorders	0.88	(0.74, 1.06)	-1.60	(-3.95, 0.76)
Deficiency anemias	0.97	(0.81, 1.17)	-0.37	(-2.80, 2.06)
Depression	**0.80**	(0.67, 0.94)	**-2.95**	(-5.09, -0.81)
Renal disease	1.08	(0.81, 1.43)	1.00	(-2.66, 4.66)

Peripheral artery or vascular disease	**0.79**	(0.64, 0.97)	**-3.09**	(-5.74, -0.44)
North Central (ref: Northeast)	1.00	(0.81, 1.23)	-0.03	(-2.53, 2.48)
South (ref: Northeast)	**0.76**	(0.63, 0.92)	**-3.61**	(-6.02, -1.20)
West (ref: Northeast)	1.21	(0.95, 1.55)	2.19	(-0.62, 5.01)

Table 3.10. Conditional quantile regression results for PDC (adherence), females

	Q10	Q20	Q30	Q40
Clopidogrel, generic (ref: clopidogrel, brand)	-0.06	-2.69	-1.81	-0.37
Prasugrel (ref: clopidogrel, brand)	-2.23	**-4.60**	**-4.03**	**-1.60**
Ticagrelor (ref: clopidogrel, brand)	-0.69	**-6.22**	**-5.47**	**-2.38**
Age	**0.61**	**0.36**	**0.23**	**0.10**
Charlson Comorbidity Index	-1.14	**-0.67**	**-0.47**	-0.15
Fee-for-service (ref: managed care)	-1.34	0.04	0.88	0.20
Incident DES inpatient setting	-3.32	-1.55	-0.65	-0.38
Incident DES due to STEMI (ref: unstable angina)	**6.51**	**3.39**	1.26	0.60
Incident DES due to NSTEMI (ref: unstable angina)	**5.57**	2.57	1.92	0.77
Baseline outpatient visits	**-0.17**	**-0.16**	**-0.09**	**-0.04**
Baseline inpatient visits	1.06	0.04	-1.92	**-1.88**
Baseline emergency room visits	-1.18	**-2.28**	**-0.98**	**-0.68**
Baseline unique medications, ≥4 and <8 (ref: <4)	**5.24**	**3.00**	1.77	0.85
Baseline unique medications, ≥8 (ref: <4)	**8.19**	**5.09**	**2.89**	**1.35**
Anticoagulant indication	2.66	2.53	0.85	0.34
Hyperlipidemia	3.21	-0.26	0.34	0.01
Valvular disease	-2.22	0.51	0.45	0.33
Hypertension	-3.15	-0.73	-0.56	-0.52
Chronic pulmonary disease	-1.38	-0.92	-0.68	-0.07
Diabetes without complications	-2.63	**-3.56**	**-3.06**	**-1.46**
Diabetes with complications	**-8.70**	**-4.08**	**-3.10**	**-1.51**
Hypothyroidism	0.63	0.72	0.13	-0.17
Obesity	0.92	-0.25	0.21	0.13
Fluid & electrolyte disorders	-3.66	-2.40	-1.01	-0.59
Deficiency anemias	0.55	-2.03	-1.17	-0.69
Depression	-2.95	**-2.73**	-1.74	-0.79
Renal disease	2.51	3.42	2.07	0.83
Peripheral artery or vascular disease	**-7.37**	**-4.66**	**-3.65**	**-2.34**
North Central (ref: Northeast)	1.57	0.00	0.03	0.35
South (ref: Northeast)	-4.23	**-5.63**	**-3.75**	**-1.32**
West (ref: Northeast)	5.73	0.88	1.12	0.47
Constant	31.56	66.09	79.93	90.09

DES, drug eluting stent; PDC, proportion of days covered

Boldfaced estimates indicated statistical significance (p-value ≤ 0.05)

Table 3.11. Unconditional quantile regression results for PDC (adherence), females

	Q10	Q20	Q30	Q40
Clopidogrel, generic (ref: clopidogrel, brand)	-0.83	-0.87	-0.58	-0.17
Prasugrel (ref: clopidogrel, brand)	-0.29	-1.32	**-5.03**	**-1.01**
Ticagrelor (ref: clopidogrel, brand)	0.04	-1.74	**-7.62**	**-1.46**
Age	**0.16**	**0.17**	**0.39**	**0.06**
Charlson Comorbidity Index	**-0.55**	-0.18	-0.55	**-0.11**
Fee-for-service (ref: managed care)	0.03	0.23	1.05	-0.01
Incident DES inpatient setting	-1.15	-0.84	-2.03	-0.11
Incident DES due to STEMI (ref: unstable angina)	**3.28**	**1.42**	**3.07**	**0.54**
Incident DES due to NSTEMI (ref: unstable angina)	1.41	0.24	**4.33**	**0.69**
Baseline outpatient visits	**-0.08**	**-0.06**	**-0.09**	**-0.01**
Baseline inpatient visits	1.79	-0.28	-3.43	-0.40
Baseline emergency room visits	-1.08	-0.43	-1.14	-0.14
Baseline unique medications, ≥4 and <8 (ref: <4)	**1.94**	1.13	**3.56**	**0.63**
Baseline unique medications, ≥8 (ref: <4)	**3.34**	**2.15**	**5.32**	**0.73**
Anticoagulant indication	**2.49**	1.14	0.97	0.28
Hyperlipidemia	1.07	0.14	0.15	0.00
Valvular disease	-1.79	-0.43	0.39	0.39
Hypertension	-0.54	**-0.96**	-0.76	**-0.38**
Chronic pulmonary disease	-0.94	-0.11	-0.69	-0.20
Diabetes without complications	-1.35	**-1.51**	**-5.12**	**-0.93**
Diabetes with complications	-1.43	-1.52	**-4.06**	-0.30
Hypothyroidism	0.29	0.16	0.25	-0.06
Obesity	0.21	0.10	-0.06	0.25
Fluid & electrolyte disorders	-2.39	-1.01	-2.86	-0.51
Deficiency anemias	0.52	-0.16	-1.42	-0.17
Depression	-0.88	**-1.46**	**-3.05**	**-0.43**
Renal disease	1.54	0.63	3.37	0.70
Peripheral artery or vascular disease	-2.37	**-1.77**	**-5.25**	**-1.01**
North Central (ref: Northeast)	-0.71	0.08	0.31	0.04
South (ref: Northeast)	**-2.16**	**-1.71**	**-6.82**	**-0.92**
West (ref: Northeast)	1.21	1.22	2.03	0.48
Constant	57.62	74.67	83.16	93.28

DES, drug eluting stent; PDC, proportion of days covered

Boldfaced estimates indicated statistical significance (p-value ≤ 0.05)

Table 3.12. Logistic regression for adherence (PDC≥80%), age≥55

Variables	Odds ratio	95% CI	Average marginal effect (dy/dx)	95% CI for marginal effects
Clopidogrel, generic (ref: clopidogrel, brand)	1.04	(0.89, 1.22)	0.45	(-1.35, 2.24)
Prasugrel (ref: clopidogrel, brand)	0.95	(0.83, 1.08)	-0.61	(-2.09, 0.87)
Ticagrelor (ref: clopidogrel, brand)	0.84	(0.70, 1.01)	-2.10	(-4.30, 0.09)
Age	**1.02**	(1.01, 1.04)	**0.25**	(0.08, 0.42)
Male	1.02	(0.93, 1.12)	0.24	(-0.86, 1.34)
Charlson Comorbidity Index	**0.95**	(0.93, 0.98)	**-0.56**	(-0.88, -0.25)
Fee-for-service (ref: managed care)	1.02	(0.91, 1.14)	0.22	(-1.13, 1.57)
Incident DES inpatient setting	1.01	(0.92, 1.11)	0.12	(-1.01, 1.25)
Incident DES due to STEMI (ref: unstable angina)	**1.27**	(1.12, 1.45)	**2.82**	(1.35, 4.29)
Incident DES due to NSTEMI (ref: unstable angina)	1.11	(0.98, 1.26)	1.25	(-0.21, 2.71)
Baseline outpatient visits	**1.00**	(0.99, 1.00)	**-0.05**	(-0.09, -0.01)
Baseline inpatient visits	0.95	(0.80, 1.11)	-0.65	(-2.54, 1.23)
Baseline emergency room visits	0.95	(0.88, 1.02)	-0.63	(-1.46, 0.21)
Baseline unique medications, ≥4 and <8 (ref: <4)	**1.14**	(1.02, 1.27)	**1.61**	(0.22, 3.00)
Baseline unique medications, ≥8 (ref: <4)	**1.40**	(1.24, 1.58)	**3.93**	(2.45, 5.41)
Anticoagulant indication	0.91	(0.79, 1.05)	-1.12	(-2.75, 0.52)
Hyperlipidemia	1.05	(0.95, 1.15)	0.52	(-0.55, 1.59)
Valvular disease	0.90	(0.78, 1.04)	-1.19	(-2.88, 0.49)
Hypertension	**0.86**	(0.79, 0.95)	**-1.69**	(-2.77, -0.61)
Chronic pulmonary disease	1.01	(0.89, 1.14)	0.08	(-1.37, 1.53)
Diabetes without complications	**0.87**	(0.79, 0.97)	**-1.58**	(-2.8, -0.37)
Diabetes with complications	0.91	(0.78, 1.07)	-1.09	(-2.92, 0.74)
Hypothyroidism	1.07	(0.94, 1.21)	0.74	(-0.76, 2.24)
Obesity	1.11	(0.99, 1.24)	1.23	(-0.06, 2.52)
Fluid & electrolyte disorders	0.87	(0.76, 1.00)	-1.56	(-3.17, 0.04)
Deficiency anemias	**0.85**	(0.74, 0.97)	**-1.95**	(-3.57, -0.33)

Depression	**0.80**	(0.70, 0.92)	**-2.55**	(-4.15, -0.95)
Renal disease	0.97	(0.81, 1.16)	-0.33	(-2.43, 1.77)
Peripheral artery or vascular disease	**0.86**	(0.75, 0.99)	**-1.70**	(-3.31, -0.08)
North Central (ref: Northeast)	0.99	(0.87, 1.13)	-0.06	(-1.48, 1.35)
South (ref: Northeast)	**0.79**	(0.70, 0.88)	**-2.88**	(-4.24, -1.53)
West (ref: Northeast)	1.12	(0.97, 1.30)	1.19	(-0.35, 2.72)

Table 3.13. Conditional quantile regression results for PDC (adherence), age≥55

	Q10	Q20	Q30	Q40
Clopidogrel, generic (ref: clopidogrel, brand)	2.49	1.10	0.46	0.21
Prasugrel (ref: clopidogrel, brand)	0.11	**-2.20**	**-1.36**	-0.33
Ticagrelor (ref: clopidogrel, brand)	-0.41	**-4.17**	**-3.43**	**-1.02**
Age	**0.69**	**0.27**	**0.17**	**0.06**
Male	-0.81	0.48	0.42	0.13
Charlson Comorbidity Index	**-2.07**	**-0.90**	**-0.41**	**-0.13**
Fee-for-service (ref: managed care)	0.89	**1.78**	0.45	0.05
Incident DES inpatient setting	-0.22	-0.17	0.02	0.11
Incident DES due to STEMI (ref: unstable angina)	**5.28**	**2.76**	0.90	0.26
Incident DES due to NSTEMI (ref: unstable angina)	**3.94**	**2.21**	0.79	0.17
Baseline outpatient visits	-0.03	**-0.07**	**-0.06**	**-0.03**
Baseline inpatient visits	-2.47	-1.27	-1.14	**-1.59**
Baseline emergency room visits	**-2.35**	**-1.28**	-0.53	**-0.48**
Baseline unique medications, ≥4 and <8 (ref: <4)	**3.97**	1.44	**0.98**	0.22
Baseline unique medications, ≥8 (ref: <4)	**8.85**	**4.35**	**1.93**	**0.51**
Anticoagulant indication	-3.08	-0.77	-0.47	0.09
Hyperlipidemia	1.21	1.09	0.14	0.04
Valvular disease	-4.21	-1.58	-0.70	-0.02
Hypertension	**-3.94**	-1.32	-0.42	-0.08
Chronic pulmonary disease	-0.76	-0.88	-0.77	-0.09
Diabetes without complications	-2.66	**-2.39**	**-1.46**	**-0.31**
Diabetes with complications	-4.13	-1.99	**-2.47**	**-0.69**
Hypothyroidism	1.58	0.23	0.29	0.05
Obesity	1.61	**1.71**	**0.81**	0.28
Fluid & electrolyte disorders	-2.63	-1.98	-1.23	-0.36
Deficiency anemias	-2.80	**-2.67**	**-1.01**	-0.35
Depression	**-4.46**	**-3.27**	**-2.75**	**-0.68**
Renal disease	2.04	1.04	0.97	0.18
Peripheral artery or vascular disease	-1.74	**-2.86**	**-2.61**	**-0.67**
North Central (ref: Northeast)	0.70	-0.75	-0.20	-0.03
South (ref: Northeast)	**-5.23**	**-4.64**	**-2.36**	**-0.55**
West (ref: Northeast)	2.74	-0.42	0.06	0.04
Constant	26.66	69.84	84.04	92.53

DES, drug eluting stent; PDC, proportion of days covered

Boldfaced estimates indicated statistical significance (p-value ≤ 0.05)

Table 3.14. Unconditional quantile regression results for PDC (adherence), age≥55

	Q10	Q20	Q30	Q40
Clopidogrel, generic (ref: clopidogrel, brand)	0.30	1.03	0.77	**0.29**
Prasugrel (ref: clopidogrel, brand)	0.47	**-3.31**	**-1.64**	**-0.39**
Ticagrelor (ref: clopidogrel, brand)	0.39	**-5.48**	**-3.84**	**-0.82**
Age	**0.13**	**0.45**	**0.21**	**0.06**
Male	-0.44	**2.21**	0.40	**0.16**
Charlson Comorbidity Index	**-0.37**	**-1.26**	**-0.39**	**-0.11**
Fee-for-service (ref: managed care)	0.09	2.89	0.68	-0.01
Incident DES inpatient setting	-0.29	0.16	0.17	**0.17**
Incident DES due to STEMI (ref: unstable angina)	**2.01**	**3.86**	**0.98**	**0.26**
Incident DES due to NSTEMI (ref: unstable angina)	**0.93**	**3.04**	0.77	**0.23**
Baseline outpatient visits	-0.01	**-0.14**	**-0.04**	**-0.01**
Baseline inpatient visits	-0.68	-2.69	-1.26	-0.20
Baseline emergency room visits	-0.56	-0.87	-0.59	-0.14
Baseline unique medications, ≥4 and <8 (ref: <4)	0.61	2.18	0.83	**0.20**
Baseline unique medications, ≥8 (ref: <4)	**1.70**	**6.61**	**1.96**	**0.43**
Anticoagulant indication	-0.22	-1.25	-0.09	0.04
Hyperlipidemia	0.47	1.32	0.17	0.07
Valvular disease	-0.94	-1.78	-0.57	-0.07
Hypertension	-0.50	**-2.49**	**-0.76**	-0.10
Chronic pulmonary disease	-0.33	-0.77	-0.73	-0.18
Diabetes without complications	**-0.98**	**-3.44**	**-1.55**	**-0.42**
Diabetes with complications	-0.60	-3.91	**-1.31**	-0.13
Hypothyroidism	0.22	0.62	0.17	0.06
Obesity	0.28	**2.95**	**1.28**	**0.25**
Fluid & electrolyte disorders	-0.76	**-4.08**	-0.97	-0.19
Deficiency anemias	-0.19	-2.09	-0.85	-0.21
Depression	-1.00	**-5.29**	**-2.15**	**-0.51**
Renal disease	0.30	1.53	0.73	0.14
Peripheral artery or vascular disease	-0.45	**-5.16**	**-1.89**	**-0.43**
North Central (ref: Northeast)	0.06	0.12	-0.33	-0.09
South (ref: Northeast)	**-0.77**	**-5.85**	**-2.58**	**-0.55**
West (ref: Northeast)	**0.92**	0.75	0.41	0.17
Constant	58.37	75.14	82.20	93.23

DES, drug eluting stent; PDC, proportion of days covered

Boldfaced estimates indicated statistical significance (p-value ≤ 0.05)

Table 3.15. Logistic regression for adherence (PDC≥80%), age<55

Variables	Odds ratio	95% CI	Average marginal effect (dy/dx)	95% CI for marginal effects
Clopidogrel, generic (ref: clopidogrel, brand)	0.92	(0.77, 1.11)	-0.99	(-3.27, 1.29)
Prasugrel (ref: clopidogrel, brand)	**0.82**	(0.71, 0.94)	**-2.67**	**(-4.49, -0.85)**
Ticagrelor (ref: clopidogrel, brand)	**0.76**	(0.62, 0.94)	**-3.63**	**(-6.42, -0.84)**
Age	**1.02**	(1.02, 1.03)	**0.32**	**(0.21, 0.44)**
Male	**1.14**	(1.02, 1.28)	**1.77**	**(0.25, 3.28)**
Charlson Comorbidity Index	**0.95**	(0.92, 0.98)	**-0.71**	**(-1.18, -0.24)**
Fee-for-service (ref: managed care)	1.13	(0.99, 1.28)	1.62	(-0.08, 3.32)
Incident DES inpatient setting	1.07	(0.94, 1.20)	0.85	(-0.78, 2.48)
Incident DES due to STEMI (ref: unstable angina)	**1.18**	(1.03, 1.34)	**2.16**	**(0.45, 3.87)**
Incident DES due to NSTEMI (ref: unstable angina)	1.10	(0.96, 1.26)	1.23	(-0.60, 3.06)
Baseline outpatient visits	1.00	(0.99, 1.00)	-0.06	(-0.11, 0.00)
Baseline inpatient visits	**0.80**	(0.67, 0.97)	**-2.93**	**(-5.42, -0.44)**
Baseline emergency room visits	0.95	(0.87, 1.04)	-0.68	(-1.93, 0.56)
Baseline unique medications, ≥4 and <8 (ref: <4)	1.07	(0.95, 1.20)	0.87	(-0.73, 2.47)
Baseline unique medications, ≥8 (ref: <4)	1.15	(1.00, 1.32)	1.84	(-0.01, 3.69)
Anticoagulant indication	1.08	(0.86, 1.35)	1.01	(-1.99, 4.02)
Hyperlipidemia	1.03	(0.93, 1.14)	0.35	(-1.03, 1.74)
Valvular disease	**0.76**	(0.62, 0.93)	**-3.66**	**(-6.28, -1.03)**
Hypertension	**0.82**	(0.74, 0.91)	**-2.70**	**(-4.07, -1.32)**
Chronic pulmonary disease	0.94	(0.80, 1.09)	-0.89	(-2.97, 1.18)
Diabetes without complications	**0.81**	(0.71, 0.92)	**-2.87**	**(-4.57, -1.17)**
Diabetes with complications	0.91	(0.74, 1.12)	-1.21	(-3.94, 1.53)
Hypothyroidism	1.00	(0.85, 1.19)	0.04	(-2.18, 2.27)
Obesity	1.11	(0.98, 1.26)	1.45	(-0.21, 3.11)
Fluid & electrolyte disorders	0.91	(0.77, 1.07)	-1.33	(-3.54, 0.88)
Deficiency anemias	1.07	(0.88, 1.30)	0.91	(-1.66, 3.47)
Depression	**0.82**	(0.70, 0.97)	**-2.63**	**(-4.83, -0.43)**
Renal disease	1.09	(0.84, 1.41)	1.09	(-2.40, 4.58)

Peripheral artery or vascular disease	0.91	(0.74, 1.11)	-1.33	(-4.08, 1.41)
North Central (ref: Northeast)	1.01	(0.87, 1.18)	0.12	(-1.77, 2.00)
South (ref: Northeast)	**0.76**	(0.67, 0.88)	**-3.61**	**(-5.38, -1.84**)
West (ref: Northeast)	0.94	(0.79, 1.11)	-0.84	(-2.98, 1.30)

Table 3.16. Conditional quantile regression results for PDC (adherence), age<55

	Q10	Q20	Q30	Q40
Clopidogrel, generic (ref: clopidogrel, brand)	-0.95	-2.10	**-2.25**	-0.72
Prasugrel (ref: clopidogrel, brand)	-2.44	**-4.67**	**-4.78**	**-1.85**
Ticagrelor (ref: clopidogrel, brand)	-3.16	**-5.91**	**-5.33**	**-2.57**
Age	**0.40**	**0.38**	**0.21**	**0.08**
Male	**4.89**	1.36	0.55	0.00
Charlson Comorbidity Index	**-1.71**	**-0.86**	-0.27	-0.13
Fee-for-service (ref: managed care)	2.08	**2.24**	**1.57**	0.18
Incident DES inpatient setting	1.15	1.36	1.16	0.52
Incident DES due to STEMI (ref: unstable angina)	**4.45**	**2.59**	1.28	0.32
Incident DES due to NSTEMI (ref: unstable angina)	**4.67**	2.15	0.10	0.17
Baseline outpatient visits	-0.14	**-0.17**	**-0.09**	**-0.04**
Baseline inpatient visits	0.23	-3.23	**-3.38**	**-4.19**
Baseline emergency room visits	-2.15	**-1.69**	**-0.89**	**-0.49**
Baseline unique medications, ≥4 and <8 (ref: <4)	2.91	1.44	0.69	0.21
Baseline unique medications, ≥8 (ref: <4)	**4.61**	1.81	0.52	0.26
Anticoagulant indication	3.24	-0.86	0.82	0.31
Hyperlipidemia	2.35	0.17	0.46	0.30
Valvular disease	**-6.98**	**-5.27**	**-3.81**	-1.12
Hypertension	**-6.22**	**-2.27**	**-1.22**	-0.43
Chronic pulmonary disease	-4.36	-2.24	-0.86	-0.29
Diabetes without complications	-2.62	**-3.70**	**-4.09**	**-1.72**
Diabetes with complications	-1.24	-2.63	-0.83	**-1.82**
Hypothyroidism	2.04	0.61	-0.42	-0.24
Obesity	2.04	1.69	0.35	-0.08
Fluid & electrolyte disorders	-4.37	-0.92	-0.65	-0.36
Deficiency anemias	1.86	0.31	0.07	-0.11
Depression	**-5.65**	**-4.70**	**-2.67**	**-1.57**
Renal disease	1.92	0.35	-0.31	-1.01
Peripheral artery or vascular disease	**-9.30**	-0.47	-1.98	**-1.50**
North Central (ref: Northeast)	0.36	-0.81	-0.50	-0.12
South (ref: Northeast)	-5.32	**-5.26**	**-4.06**	**-1.54**
West (ref: Northeast)	-2.09	-1.87	-1.14	-0.26
Constant	37.64	61.41	79.82	91.87

DES, drug eluting stent; PDC, proportion of days covered

Boldfaced estimates indicated statistical significance (p-value ≤ 0.05)

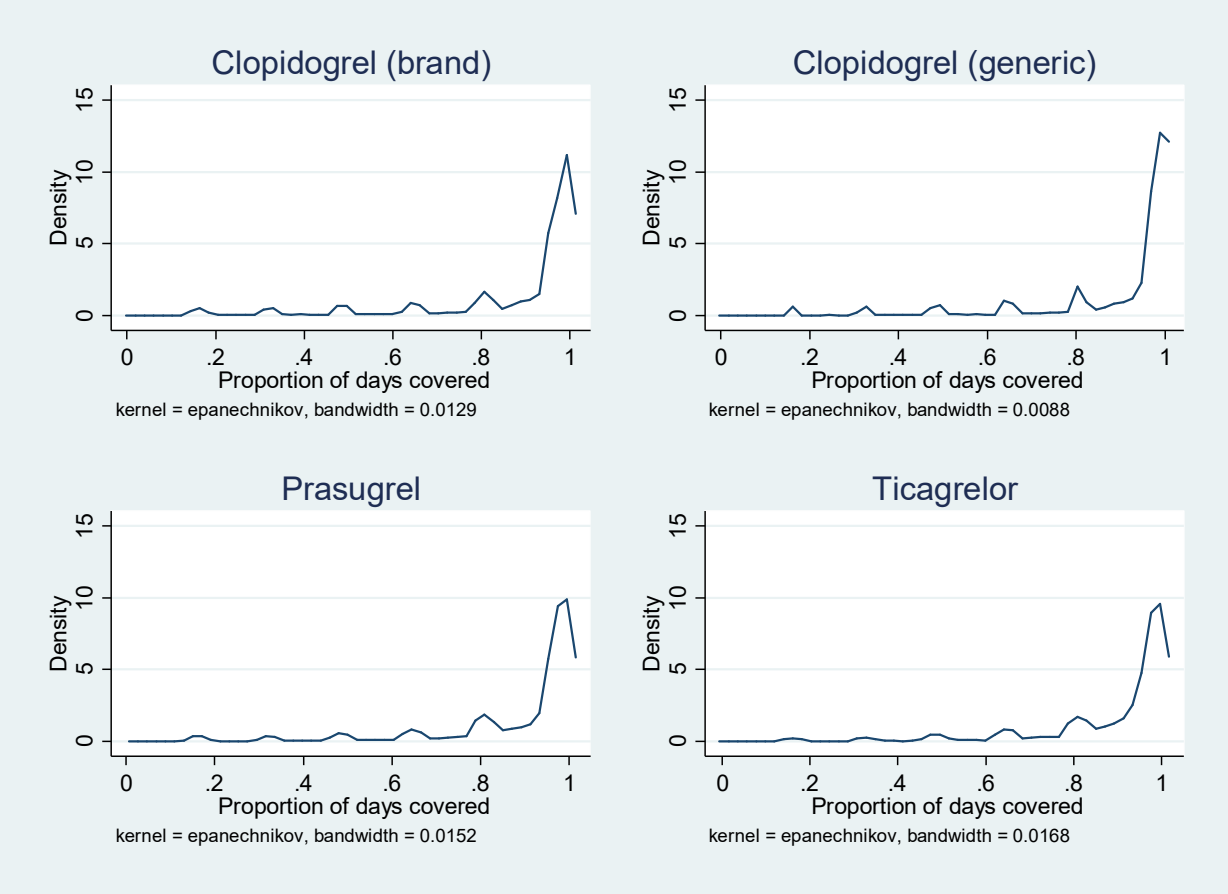
Table 3.17. Unconditional quantile regression results for PDC (adherence), age<55

	Q10	Q20	Q30	Q40
Clopidogrel, generic (ref: clopidogrel, brand)	-0.89	-0.71	-1.19	-0.28
Prasugrel (ref: clopidogrel, brand)	-0.90	**-1.57**	**-5.51**	**-1.32**
Ticagrelor (ref: clopidogrel, brand)	-0.75	**-1.93**	**-6.85**	**-1.86**
Age	**0.14**	**0.17**	**0.33**	**0.06**
Male	**1.13**	**0.90**	1.52	0.17
Charlson Comorbidity Index	**-0.55**	**-0.38**	**-0.67**	**-0.11**
Fee-for-service (ref: managed care)	0.27	0.78	**3.16**	0.26
Incident DES inpatient setting	0.07	0.44	0.76	0.27
Incident DES due to STEMI (ref: unstable angina)	**1.70**	**1.12**	**2.66**	**0.50**
Incident DES due to NSTEMI (ref: unstable angina)	0.83	0.67	1.70	0.17
Baseline outpatient visits	-0.05	**-0.04**	**-0.07**	**-0.02**
Baseline inpatient visits	-1.53	**-2.34**	-3.23	-0.48
Baseline emergency room visits	-0.76	-0.43	-0.84	-0.06
Baseline unique medications, ≥4 and <8 (ref: <4)	**1.00**	0.45	0.30	0.24
Baseline unique medications, ≥8 (ref: <4)	**1.98**	**0.97**	0.47	0.14
Anticoagulant indication	0.51	0.44	-0.03	0.13
Hyperlipidemia	0.52	0.14	0.83	0.15
Valvular disease	**-2.83**	**-2.26**	-3.18	-0.46
Hypertension	**-1.47**	**-1.33**	**-2.28**	**-0.61**
Chronic pulmonary disease	**-1.58**	-0.40	-1.59	-0.16
Diabetes without complications	-1.10	**-1.48**	**-4.77**	**-0.94**
Diabetes with complications	0.34	-0.80	-1.77	-0.22
Hypothyroidism	0.82	0.01	-0.07	-0.20
Obesity	0.75	**0.80**	0.46	0.09
Fluid & electrolyte disorders	**-2.56**	-0.75	-1.60	-0.22
Deficiency anemias	1.15	0.52	-0.07	0.21
Depression	-1.78	**-1.46**	**-3.65**	**-0.69**
Renal disease	0.35	0.58	0.21	-0.02
Peripheral artery or vascular disease	-2.09	-0.74	-3.13	**-0.74**
North Central (ref: Northeast)	-0.44	0.11	-0.74	-0.06
South (ref: Northeast)	**-2.01**	**-1.76**	**-6.25**	**-1.13**
West (ref: Northeast)	-1.22	-0.39	-1.33	-0.21
Constant	57.86	73.17	84.37	93.21

DES, drug eluting stent; PDC, proportion of days covered

Boldfaced estimates indicated statistical significance (p-value ≤ 0.05)

Figure 3.1. Unconditional distribution of proportion of days covered



References

1. Amsterdam E, Wenger N, Brindis R, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;130(25):e344-426.
2. Levine G, Bates E, Blankenship J, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *Circulation.* 2016;133(11):1135-1147.
3. Levine G, Bates E, Bittl J, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation.* 2016;134(10):e123-155.
4. Mehta S, Yusuf S, Peters R, Bertrand M, Lewis B, Natarajan M. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet.* 2001;358(9281):527-533.
5. Yusuf S, Zhao F, Mehta S, Chrolavicius S, Anand S. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001;345:494-502.
6. Wallentin L, Becker R, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045-1057.
7. Wiviott S, Braunwald E, McCabe C, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357:2001-2015.
8. Gaubert M, Laine M, Richard T, et al. Effect of ticagrelor-related dyspnea on compliance with therapy in acute coronary syndrome patients. *Int J Cardiol.* 2014;173:120-121.
9. Melloni C, Alexander K, Fang-Shu O, et al. Predictors of early discontinuation of evidence-based medicine after acute coronary syndrome. *Am J Cardiol.* 2009;104:175-181.
10. Muntner P, Mann D, Woodward M, et al. Predictors of low clopidogrel adherence following percutaneous coronary intervention. 2011.
11. Nordstrom B, Simeone J, Zhao Z, et al. Adherence and persistence with prasugrel following acute coronary syndrome with percutaneous coronary intervention. *Am J Cardiovasc Drugs.* 2013;13:263-271.
12. Pallares M, Powers E, Zwerner P, Fowler A, Reeves R, Nappi J. Barriers to clopidogrel adherence following placement of drug-eluting stents. *Ann Pharmacother.* 2009;43:259-267.
13. Zanchin T, Temperli F, Karagiannis A, et al. Frequency, reasons, and impact of premature ticagrelor discontinuation in patients underdoing coronary revascularization in routine clinical practice. *Circ cardiovasc Interv.* 2018;11:e006132.
14. Zeymer U, Cully M, Hochadel M, REAL-TICA Investigators. Adherence to dual antiplatelet therapy with ticagrelor in patients with acute coronary syndromes treated with percutaneous coronary intervention in real life. Results of the REAL-TICA registry. *Eur Heart J Cardiovasc Pharmacother.* 2018;4:205-2010.

15. Zhu B, Zhao Z, McCollam P, et al. Factors associated with clopidogrel use, adherence, and persistence in patients with acute coronary syndromes undergoing percutaneous coronary intervention. *Curr Med Res Opin.* 2011;27:633-641.
16. Firpo S, Fortin N, Lemieux T. Unconditional quantile regression. *Econometrica.* 2007;77:953-973.
17. Borah B, Basu A. Highlighting differences between conditional and unconditional quantile regression approaches through an application to assess medication adherence. *Health Econ.* 2013;22:1052-1070.
18. Dayoub E, Seigerman M, Tuteja S, et al. Trends in platelet adenosine diphosphate P2Y12 receptor inhibitor use and adherence among antiplatelet-naive patients after percutaneous coronary intervention, 2008-2016. *JAMA Intern Med.* 2018;178(7):943-950.
19. National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP). *Calculating proportion of days covered (PDC) for antihypertensive and antidiabetic medications: an evaluation guide for grantees.* Centers for Disease Control and Prevention (CDC);2015.
20. Le Cook B, Manning W. Thinking beyond the mean: a practical guide for using quantile regression methods for health services research. *Shanghai Arch Psychiatry.* 2013;25(1):55-59.
21. Koenker R, Bassett G. Regression quantiles. *Econometrica.* 1978;46:33-50.
22. George J, Shalansky S. Predictors of refill non-adherence in patients with heart failure. *Brit J Clin Pharmacol.* 2007;63:488-493.
23. Gao X, Nau D, Rosenbluth S, Scott V, Woodward C. The relationship of disease severity, health beliefs and medication adherence among HIV patients. *AIDS Care.* 2000;12:387-398.

Appendix

Appendix A.1.1. Formal models behind local instrumental variable (LIV) methods, marginal treatment effects, and person-centered treatment (PeT) effects

Assume the following model of potential outcomes:

$$Y_i = D_i Y_{1i} + (1-D_i) Y_{0i} \quad (1)$$

where D_i=0 represents untreated (i.e. clopidogrel), Di=1 represents treated (i.e. newer $P2Y_{12}$ inhibitor), Y_{0i} represents the outcome (i.e. MACE or major bleed) in the untreated state and Y_{1i} represents the outcome in the treated state.

This can then be expressed as

$$Y_{ji} = \mu_j(X_{Oi}, X_{Ui}, v_i) \text{ for } j=0,1 \quad (2)$$

where X_{Oi} represents a vector of observed characteristics, X_{Ui} represents a vector of unobserved characteristics correlated with treatment decision, and v_i represents all unobserved random variables.[1]
As in Heckman and Vytlacil (1999)[2], assume the following latent variable model where the treatment assignment is generated by a latent variable D_i*:

$$D_i^* = \mu_D(X_{oi}, Z_i) - U_{Di} \quad (3)$$

where X_{oi} represents a vector of observed variables, Zi represents a vector of observed random variables (i.e. instruments), U_{Di} represents unobserved variables, and μ_D is an unknown function
If the patient perceives some benefit from treatment choice, they will choose treatment. In other words, D_i=1 if $D_i^* \geq 0$ and D_i=0 if D_i^*<0. Through this model, a marginal patient can be identified as someone whose levels of observed and unobserved characteristics are balanced such that they are indifferent to taking clopidogrel or newer $P2Y_{12}$ inhibitor. Then, by shifting the IV level a tiny bit, for example from 0.50 to 0.51, a marginal treatment effect (MTE) can be captured for this level of IV. This is because the change in IV is so small that the risk factors (observed and unobserved) should be the same between these two levels such that the only reason for changing the treatment choice is due to living in a particular MSA with a particular treatment rate of newer $P2Y_{12}$ inhibitor. Thus, any change in average outcomes can be attributed to the marginal patients who made different treatment choices because the level of IV changed. However, these are still hypothetical individuals that cannot be identified by the analyst.
With more than 300 MSAs and 14 six-month study periods, the IV in this study can take on over 4200 distinct values, resulting in a continuous IV measure. By using a continuous IV, different levels of the instrument can be used to obtain MTEs over the entire distribution of the IV. PeT effects extend the LIV methods to characterize patients based on their observed and unobserved characteristics.[1]

$$\text{PeT}(x_o, z \mid D=1) = \frac{1}{P(xo,z)} \int_0^{P(xo,z)} MTE\ (xo, v)\ dv \quad (4)$$

$$\text{PeT}(x_o, z \mid D=0) = \frac{1}{1 - P(xo,z)} \int_{P(xo,z)}^{1} MTE\ (xo, v)\ dv \quad (5)$$

where x_o represents the observed variables and v represents all unobserved random variables. The PeT effect for those who take newer $P2Y_{12}$ inhibitor is the treatment on the treated (TT) conditional on xo and z, while for those taking clopidogrel, the PeT effect is the treatment on the untreated (TUT) conditional on xo and z. PeT effects explain more individual-level variability because they incorporate information about the treatment choice (D) and the circumstance in which it was made (Z).[1]

For further clarification and explanation, an excellent summary is provided in a recent paper's supplementary material using the same methods.[3]

References

1. Basu A. Estimating person-centered treatment (PeT) effects using instrumental variables: an application to evaluating prostate cancer treatments. *J Appl Econ (Chichester Engl).* 2014;29(4):671-691.
2. Heckman J, Vytlacil E. Local instrumental variables and latent variable models for identifying and bounding treatment effects. *Proc Natl Acad Sci.* 1999;96(8):4730-4734.
3. Grieve R, O'Neill S, Basu A, Keele L, Rowe K, Harris S. Analysis of benefit of intensive care unit transfer to deteriorating ward patients: a patient-centered approach to clinical evaluation (supplementary online content). *JAMA Network Open.* 2019;2(2):e187704.

VITA

Kangho Suh is a fifth-year PhD candidate in The Comparative Health Outcomes, Policy, and Economics (CHOICE) Institute at the University of Washington. Prior to his time at The CHOICE Institute, Kangho received his Masters in Pharmacy Administration from The University of Texas at Austin (UT-Austin) and his PharmD from the Ernest Mario School of Pharmacy, Rutgers University. Kangho also completed a health economics and outcomes research fellowship with UT-Austin, Scott and White Health Plan, and Novartis Pharmaceuticals. His research interests include comparative and cost effectiveness research and pharmacoeconomics.