COMPARATIVE EFFECTIVENESS AND SAFETY OF P2Y12 INHIBITORS IN THE SECONDARY PROPHYLAXIS OF ACUTE CORONARY SYNDROME

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Abstract

One of the major problems among patients suffering from coronary heart disease especially acute coronary syndrome (ACS) is recurrent cardiovascular events following revascularization. Therefore, treatment with P2Y12 receptor antagonists and aspirin, widely known as dual antiplatelet therapy (DAPT), is strongly recommended as secondary prophylaxis following revascularization. DAPT has been shown to be effective at reducing recurrent events and rehospitalization. However, it has also been shown to increase the risk of major bleeding events. Clopidogrel, a P2Y12 inhibitor, has been utilized for ACS management since its approval in 1997 with two additional P2Y12 agents approved by the US Food and Drug Administration in 2009 (prasugrel) and 2011 (ticagrelor). Compared with clopidogrel these newer agents have more potent and predictable antiplatelet aggregation profiles, attributed to consistent pharmacokinetics and dynamics. However, the evidence related to their safety and efficacy/effectiveness is inconsistent. Moreover, the evidence from the studies conducted in the US comes from electronic health records that may not be generalizable to a broader US population. In this dissertation, we sought to assess the comparative effectiveness and safety of different P2Y12 inhibitors in patients with ACS following revascularization with percutaneous coronary intervention (PCI) using commercial claims and encounters (CCAE) and Medicare Supplement (MDCR) data samples of the MarketScan database that may represent a broader US population

In the ***first aim*** of this dissertation, we looked at the treatment patterns of different P2Y12 inhibitors among patients with coronary heart disease. Recommendations for antiplatelet treatment with P2Y12 agents after revascularization

vary across types of revascularization i.e., fibrinolysis, PCI, or coronary artery bypass grafting, and across different clinical characteristics. Aim 1 examined patterns of P2Y12 inhibitor utilization across a number of important characteristics including high bleeding risk, history of stroke/trans-ischemic attack, and associated comorbidities. Our results show that in the year 2018, ticagrelor became the most prescribed drug among patients below age 65 years compared to clopidogrel and prasugrel. We also observed an increased utilization of ticagrelor among patients managed with PCI. However, regardless of age, clopidogrel was the most commonly used drug in patients revascularized using coronary artery bypass graft. Clopidogrel use was more common than other P2Y12 inhibitors in patients with higher comorbid indices, a history of stroke/trans ischemic attacks, and in patients with a high risk of bleeding.

In the ***second and third aims,*** we assessed the effectiveness and safety of different P2Y12 inhibitors among ACS patients undergoing PCI respectively. Our results showed no difference in the primary effectiveness outcome, defined as any cardiovascular event at 30 days and 180 days observation between propensity score (PS) matched treatment cohorts in our combined CCAE and MDCR population. However, in the MDCR sample, we saw an 84% higher risk of hospitalization due to composite cardiovascular outcome in the female population associated with prasugrel compared to ticagrelor in 180 days outcome using a time to event analysis with Cox-regression hazard models. Additionally, in the CCAE sample, those who were managed with bare-metal stents (BMS) stent had a 43% lower risk of hospitalization due to composite cardiovascular outcome when prescribed prasugrel compared to ticagrelor at 180 days. We did not find any difference in hospitalizations due to composite major

bleeding identified using the Cunningham algorithm in all of the PS matched comparisons across all the groups. However, we found a significant 44% increased risk of hospitalization because of major bleeding with prasugrel compared to ticagrelor at 180 days.

This study provides useful information related to coronary heart disease management and insight into how newer agents are being utilized in a real-world US population. We show a significant increase in the use of ticagrelor in younger populations undergoing a PCI. Multiple predictors of P2Y12 inhibitor use were studied. Although antiplatelet prescription guidelines were generally followed, the use of prasugrel among patients with a history of stroke or transient ischemic attack was also observed which is contraindicated and may be worth additional investigation. Differences in the use of P2Y12 inhibitors across different patient clinical characteristics may have important policy implications and help to guide appropriate prescribing. Additionally, we observed that the female population benefited more from newer P2Y12 use in our study. Given the differential mechanism of sex on ACS prognosis, future studies are warranted to confirm this finding.

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List of Abbreviations

ABM	Andersen's Behavior Model
ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme Inhibitors
ACS	Acute Coronary Syndrome
ADP	Adenosine Diphosphate
AHA	American Heart Association
ARD	Absolute Risk Difference
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CCAE	Commercial Claims and Encounters Database
CCI	Charlson Comorbidity Index
CDHP	Consumer-Driven Health Plan
CHD	Coronary Heart Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
CPT	Current Procedural Terminology
DAPT	Dual Antiplatelet Therapy
DES	Drug Eluting Stent
DPP4	Dipeptidyl Peptidase 4 Inhibitors
EI	Elixhauser Index
EKG	Electrocardiogram
EPO	Exclusive Provider Organization
ER	Emergency Room
FDA	Food and Drug Administration
GI	Gastrointestinal
GLP-1	Glucagon Like Peptide 1 Agonist
H2RA	H2 Receptor Antagonists
HCPCS	Healthcare Common Procedure Coding System
HDHP	High-Deductible Health Plan

HER	Electronic Health Record
HMO	Health Maintenance Organization
HR	Hazard Ratio
IC	Intracranial
ICD-9 CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IHD	Ischemic Heart Disease
ITT	Intention to Treat
LBW	Low Body Weight
MACE	Major Adverse Cardiac Outcome
MDCR	Medicare Supplemental and Coordination of Benefit
MI	Myocardial Infarction
NDC	National Drug Codes
NNT	Number Needed to Treat
NSAIDS	Non-Steroidal Anti Inflammatory Drugs
NSTEMI	Non-ST Wave Elevation Myocardial Infarction
OR	Odds Ratio
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
POS	Point-of-Service
PPIs	Proton Pump Inhibitors
PPO	Preferred Provider Organization
PS	Propensity Score
RCT	Randomized Controlled Trial
SGLT	Sodium Glucose Co-Transporter Inhibitors
SIHD	Stable Ischemic Heart Disease
STEMI	ST Wave Elevation Myocardial Infarction
TIA	Transient Ischemic Attack
TZD	Thiazolidinediones
UA	Unstable Angina

CHAPTER 1: INTRODUCTION

1.1. Overview

Coronary heart disease (CHD) is common in the US affecting over 18 million Americans.[1] CHD results from atherosclerosis and in turn narrowing of coronary arteries which may cause vascular damage and thrombosis which may need revascularization of affected arteries.[2] The manifestations of CHD include stable ischemic heart disease, unstable angina, and acute myocardial infarction (MI).[3] Patients with established CHD are at increased risk of further vascular events and associated mortality,[4] which makes secondary prevention necessary in long-term management after initial CHD events.[5] CHD is an umbrella term to define coronary artery diseases; whereas, an acute form of CHD condition is known as an acute coronary syndrome (ACS) which is an emergency.

ACS is common in the US with over 780,000 patient cases resulting in approximately $150 billion in health care spending annually. The incidence of ACS increases with age although, on average, this occurs 7–10 years earlier in men compared to women.[6] The prevalence of MI is 3.0% in US adults ≥20 years of age. By age groups, males typically have a higher prevalence of MI than females. Also, the overall prevalence of angina is 3.4% in US adults ≥20 years of age.[7] Interestingly, as much as 60% of the cost of ACS is attributed to rehospitalization following an initial event highlighting the need for additional research on treatment effectiveness.[8,9] ACS involves an array of clinical presentations related to acute injury to the myocardium resulting from a sudden reduction of blood supply due to coronary artery occlusion. It is accompanied by symptomatic disease resulting in myocardium infarction, morbidity, and mortality.[10,11] ACS events present as (1) ST wave elevated myocardial infarction

(STEMI), in which complete blocking of a coronary artery for 2-4 hours takes place affecting the full thickness of myocardium [12], and (2) Non-ST wave elevated acute coronary syndrome (NSTE-ACS), which is further subdivided into (a) NSTEMI, with elevated biomarkers, and (b) unstable angina (UA), those without elevated biomarkers.[9] In NSTEMI deprivation of oxygen also occurs resulting in necrosis but not full-thickness necrosis.[12,13]

It is estimated that as many as 10% of cardiovascular events reoccur within one year of the principal ACS event resulting in a significant need for a better understanding of the long-term management of this condition.[14] Long-term management following initial revascularization to prevent recurrence of ACS involves the use of dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor i.e., clopidogrel, prasugrel, or ticagrelor.[15] DAPT with clopidogrel and aspirin has proven to have better efficacy and safety than ticlopidine (another oral P2Y12 inhibitor) in several large randomized controlled trials (RCTs) resulting in a shift toward greater clopidogrel prescribing for this purpose.[16-19] Although effective, clopidogrel-based DAPT is hampered by its slow onset of action,[20] variable inter-individual response,[21] and treatment resistance,[22-24] resulting in a high risk of treatment failure. With the introduction of newer P2Y12 inhibitors prasugrel and ticagrelor in 2009 and 2011, a further shift in prescribing is underway. These products have shown better pharmacokinetic profiles and several RCTs have shown better efficacy compared to clopidogrel with mixed evidence of safety as measured through major bleeding events.[25-29] Furthermore, observational studies comparing newer products to clopidogrel have shown inconsistent results on effectiveness and safety one year following an initial ACS event,[30-35] with a scarcity of studies assessing the risk in the US population.

1.2. Significance and Rationale

The guidelines on the specific type of P2Y12 agents' prescription and their duration differ with patient characteristics and the type of revascularization technique (Table 1.1). These recommendations are based on the results of various RCTs comparing P2Y12 agents showing distinctive efficacy and safety across patients with different characteristics and also with the type of procedure to re-vascularize the affected arteries. A summary of recommendations by ACC/AHA on the type and duration of P2Y12 inhibitors based on different characteristics is given in **Table 1.1**. A description of the factors that may be responsible for the variations in the efficacy and safety of P2Y12 inhibitors are described below:

1.2.1. Patient Characteristics

Patients with a history of cerebrovascular events and those who are at increased risk of bleeding are not recommended to be prescribed prasugrel over clopidogrel owing to safety concerns. In TRITON-TIMI 38 RCT, which studied the effect of prasugrel and clopidogrel after PCI, prasugrel use in ACS patients resulted in greater fatal bleeding compared to clopidogrel.[25] Also, in a major RCT, DAPT in ACS patients with a history of cerebrovascular events was linked to life-threatening major bleeding.[36] Additionally, a post hoc study of TRITON-TIMI 38 RCT also indicated that compared to clopidogrel, prasugrel induced significantly increased life-threatening and fatal bleeding with worse clinical outcomes in terms of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.[25] The association of major bleeding in prasugrel appears to be due to the quick onset of action and higher inhibition of platelet aggregation & activation compared to clopidogrel.[37,38] Because of the safety concerns, FDA has also

labeled prasugrel with a black box warning.[39] The current recommendations by AHA/ACC do not recommend the use of prasugrel over clopidogrel in patients with a history of stroke or TIA and high risk of bleeding; however, among those without high bleeding risk, the use of prasugrel is preferred over clopidogrel as a maintenance therapy because of better efficacy profile.[40,41]

Given differences in the presentation of ACS across patients, initial treatment recommendations to control acute events of ACS also differ**.** Among patients with STEMI presentation of ACS, reperfusion through percutaneous coronary intervention (PCI) within 12 hours of symptom onset is recommended by the American Heart Association (AHA).[42] For high-risk patients with NSTEMI/UA, an early invasive strategy through revascularization within 48 hours of presentation is recommended as an additional treatment.[43] Although initial treatment recommendation guidelines differ between patients with ACS presenting with STEMI versus NSTEMI/UA, less is known about the effect of ACS presentation on long-term medication management and health outcomes. Patients presenting with STEMI have lower rates of comorbidities, are more likely to undergo PCI, and are more often prescribed antihypertensive medications while hospitalized compared to NSTEMI patients.[44] In a study comparing the mortality risk among patients undergoing catheterization, STEMI patients also tended to have higher short term and lower long-term risk of mortality compared to NSTEMI patients.[45] Thus, the effectiveness and safety of antiplatelet drugs across STEMI and NSTEMI patients are likely to vary and should be studied distinctly. Currently, no studies have compared newer antiplatelet drugs to clopidogrel separately for STEMI and NSTEMI/UA patients in real-world practice post PCI. This proposed study is likely to fill this research gap by

studying the response across P2Y12 inhibitors separately in STEMI and NSTEMI/UA patients separately.

Another important characteristic that needs to be considered while prescribing P2Y12 inhibitors is older age because of the higher risk of bleeding in advanced age.[40] Potent P2Y12 inhibitors are associated with better efficacy; however, finding a balance in older age is challenging because of the associated higher risk of bleeding. Data related to the use of P2Y12 inhibitors is scarce; however, recently, an RCT in the Netherlands compared newer P2Y12 inhibitors (i.e., ticagrelor and prasugrel) with clopidogrel among patients with age 70 years or older.[46] This first RCT comparing newer P2Y12 inhibitors with clopidogrel in this age group reported both groups to be similar in terms of net clinical benefit; however, the use of clopidogrel was associated with a lower risk of bleeding (HR: 0.71; 95% CI (0.54-0,94) indicating clopidogrel a favorable P2Y12 inhibitor among the patients with age of at least 70 years.

Finally, the female sex has been shown to predict poor prognosis compared to males in ischemic heart disease (IHD).[47] For example, females have worse clinical outcomes compared to their male counterparts following an MI, with higher complications and mortality rates.[48] In a previous study, distinct pathophysiology by sex has been reported to be responsible for the ischemic changes in the coronary arteries. While the female population tends to suffer coronary artery microvascular dysfunction and plaque erosion resulting in thrombus establishment, the male population is believed to have plaque rupture principally responsible for a MI.[49,50]

1.2.2. Type of Revascularization

AHA/ACC guidelines differ as per the revascularization technique employed to maintain oxygen saturation in the myocardium. Among patients with recent ACS, those who are managed with pharmacological fibrinolytic therapy are recommended to be prescribed clopidogrel over prasugrel and ticagrelor. And those who are managed mechanically with PCI (i.e., using stents) are given Class I recommendation by AHA/ACC to be prescribed with any of the P2Y12 inhibitors (i.e., clopidogrel, prasugrel, or ticagrelor). In most cases, PCI with drug-eluting stents (DES) is preferred to bare metal stents[51] due to their lower association with restenosis and target vessel revascularization and is considered as the gold standard.[52-55]

1.2.3 Duration of Dual antiplatelet therapy:

For ACS patients, current ACC/AHA guidelines recommend DAPT treatment including a P2Y12 inhibitor coupled with a low dose aspirin for at least 12 months. Twelve-month treatment is recommended irrespective of the mode of revascularization (i.e., fibrinolysis, PCI, or coronary artery bypass grafting (CABG)). However, shorter duration therapy for six months is recommended for patients at high risk of bleeding.[40]

Importantly, the ideal duration of DAPT is a subject of debate especially in the era when newer generation DES are used while performing a PCI. Current recommendations for 12-month treatment with a P2Y12 inhibitor is largely based on the CURE trial (2001) in which a 12-month treatment was found favorable to reduce the risk of cardiovascular events among NSTEMI patients treated with a PCI.[56] Nevertheless, there are several studies in favor of a shorter duration of DAPT especially among the

patients managed with newer-generation DES. For example, a double-blind RCT which compared 6 months versus 12 months DAPT therapy found no difference between the two arms for stent thrombosis (HR:1.66; 95% CI (0.40-6.96) and major bleeding (HR:0.80; 95% CI (0.21-2.98).[57] Another RCT reported both 6 months and 12 months treatment not different from each other for net clinical benefit defined as a composite outcome.[58] Additionally, a systematic review conducted to assess the optimal duration of DAPT also reported no difference between 12 months and 3 to 6 months therapy as it reported no difference in the incidence of death (OR: 1.17; 95% CI (0.85-1.63), MI (OR: 0.87; 95% CI (0.65-1.18), and major bleeding (OR: 1.65; 95% CI (0.97-2.82).[59] Thus, the evidence supports the short-term treatment with DAPT among the patients managed with newer-generation DES. Given that newer-generation DES are associated with lower stent thrombosis, current AHA/ACC recommendations have also termed the shorter term DAPT as “reasonable” compared to 12 months if PCI is performed using second-generation DES.[40] As DAPT includes a P2Y12 inhibitor with two additional P2Y12 inhibitors approved by FDA, it is imperative to assess the effectiveness and safety of different P2Y12 inhibitors for a shorter duration. However, currently, there are no studies that have compared these agents for a shorter period.

Table 1. 1 Summary of Comparison of Recommendation of Type and Duration of P2Y12 Antagonists Prescribing[40,41]

Patient Population	Recommendation for P2Y12 antagonist for maintenance therapy
TYPE OF REVASCULARIZATION	
ACS managed with medical therapy alone	Clopidogrel and ticagrelor (Class I, AHA/ACC)
STEMI patients with fibrinolytic (lytic) therapy alone	Clopidogrel (Class I, AHA/ACC)
Coronary stent implantation post ACS (STEMI or NSTE-ACS)	Reasonable to use ticagrelor over clopidogrel (Class IIa)
ACS managed mechanically with PCI (i.e., using stents)	Class I recommendation for any of the P2Y12 inhibitor (i.e., clopidogrel, prasugrel, or ticagrelor)
NSTE–ACS managed with medical therapy alone (without fibrinolytic therapy or revascularization)	Reasonable to prefer ticagrelor over clopidogrel (Class IIa)
PATIENT CHARACTERISTICS	
NSTE-ACS or STEMI patients after stent implantation in those who are not at high-risk for complications due to bleeding and with no history of stroke or TIA	Reasonable to prefer prasugrel over clopidogrel (Class IIa)
ACS patients with a prior history of stroke or TIA	Prasugrel contraindicated
RECOMMENDATION FOR THE DURATION OF DAPT THERAPY	
STEMI patients treated with DAPT (in conjunction with fibrinolysis)	Clopidogrel ideally should be given for at least 12 months (Class I)
STEMI patients managed with fibrinolytic therapy not at high bleeding risk.	DAPT continuation for longer than 12 months may be reasonable (Class IIb)
ACS patients (NSTE-ACS or STEMI) after BMS or DES implantation,	Clopidogrel, prasugrel, or ticagrelor for at least 12 months (Class I)
ACS patients after DES implantation if undergoing an intracranial surgery, or develop a high risk of bleeding	Reasonable to discontinue P2Y12 inhibitor therapy after 6 months (Class IIb)

Acronyms: ACS: Acute coronary Syndrome; AHA: American Heart Association; ACC: American College of Cardiology; NSTE-ACS: non-ST wave elevated acute coronary syndrome; PCI: percutaneous coronary intervention; STEMI: ST wave elevated myocardial infarction; TIA: tans ischemic attack; DAPT: Dual antiplatelet therapy; BMS: bare-metal stent; DES: drug eluted stent.

Literature Gap

From our review of the literature, there is a discrepancy in prescription guidelines for the type and duration of P2Y12 inhibitors depending on the various clinical characteristics and the type of revascularization used to restore blood flow in the coronary arteries. The use of newer P2Y12 agents, if not contradicted, is suggested by guidelines because of a better efficacy profile compared to clopidogrel. Nevertheless, as newer P2Y12 inhibitors are associated with a higher risk of bleeding, a balance between their efficacy and safety is essential. The current recommendations caution the use of P2Y12 inhibitors in situations like high bleeding risk, stroke history, advanced age, and type of revascularization; however, the literature currently lacks studies to assess whether recommendations are followed in real-world US populations with varying clinical characteristics receiving different revascularization procedures. Additionally, the current literature lacks studies examining the effectiveness and safety of newer P2Y12 agents based on patient characteristics that may impact clinical outcomes. Another important gap in the literature not presently addressed in the evidence available from clinical trials and observational studies is the short-term treatment for DAPT following initial revascularization after an ACS event. Current AHA/ACC recommendations indicate a minimum treatment of DAPT for 6-12 months.[60] However, with the development of second-generation DES, a shorter duration of antiplatelet therapy may be desired. Currently, the literature lacks studies that have compared these agents for a shorter period in a real-world population in the US. This study examines the effectiveness and safety of these agents at a shorter duration i.e., 1 month and 6 months to know the difference between different P2Y12 inhibitors.

This study will use an observational study design to examine patterns of utilization of P2Y12 inhibitors based on various clinical characteristics as well as the comparative effectiveness and safety across P2Y12 inhibitors for the management of ACS post PCI. We use secondary claims data from the MarketScan Commercially Insured and Medicare Supplemental populations to conduct this study. Specific aims related to this study are discussed in detail in the next section.

1.3. Specific Aims

1.3.1. Study 1: Prescription Patterns of P2Y12 Inhibitors Following Revascularization in the United States: 2013-2018

Clopidogrel has been utilized for secondary CHD prophylaxis for a long time with two newer generation P2Y12 inhibitors i.e., prasugrel and ticagrelor approved by the US FDA in 2009 and 2011,[61] respectively. Secondary prophylaxis with a P2Y12 inhibitor and aspirin, termed dual antiplatelet therapy (DAPT), is strongly recommended by the AHA/ACC.[60] However, the guidelines on the type of P2Y12 agent to prescribe differ with (i) patient's clinical characteristics (i.e., high bleeding risk and history of stroke, and (ii) the type of revascularization technique (PCI, CABG, or fibrinolysis).[41] Despite these recommendations, there are currently no studies that have differentiated real-world prescribing patterns following different revascularization procedures and clinical characteristics in coronary heart disease.

The overall objective of Aim 1 was to examine differences in the prescribing of P2Y12 agents in different revascularization techniques (i.e., fibrinolysis, PCI, & CABG), and among patients at high risk of bleeding and with a history of stroke or trans-ischemic events. Additionally, we determined the predictors of utilization of one P2Y12 inhibitor over the other among CHD patients.

The specific aims of study one were:

- **Aim 1 (a):** To determine the difference in the utilization of P2Y12 inhibitors as per the technique of revascularization (Invasive versus non-invasive)

- **Aim 1 (b):** To determine the difference in the utilization of P2Y12 inhibitors among the patients at increased bleeding risk.
- **Aim 1 (c):** To determine the difference in the utilization of P2Y12 inhibitors among patients with a history of stroke or trans-ischemic attacks.
- **Aim 1 (d):** To determine if there is an adoption of newer generation P2Y12 inhibitors with time from the year 2013 to 2018.
- **Aim 1 (e):** To determine the predictors of P2Y12 inhibitor selection one over the other.

The results of this study will delineate the current prescribing patterns of these agents in as large US population with CHD. More importantly, this study will describe how the decision to prescribe a particular P2Y12 inhibitor varies with different patient characteristics including the mode of revascularization, bleeding risk, and history of stroke. Additionally, this study will add to the literature on various characteristics that predict the use of one P2Y12 inhibitor over the other. This information may have important policy implications for appropriate prescribing and better disease management with P2Y12 inhibitors.

1.3.2. Study 2: Comparative Effectiveness of P2Y12 Inhibitors for Secondary Prophylaxis in Acute Coronary Syndrome after Percutaneous Coronary Intervention

Secondary prophylaxis for recurrent ACS is essential to reduce mortality and adverse cardiovascular outcomes of ACS survivors following initial revascularization with PCI.[60] Following a PCI, long-term management to prevent recurrence of ACS involves the use of dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor

i.e., clopidogrel, prasugrel, or ticagrelor.[15] Clopidogrel-based DAPT is hampered by its slow onset of action,[20] variable inter-individual response,[21] and treatment resistance,[22-24] resulting in a high risk of treatment failure. Newer P2Y12 inhibitors including prasugrel and ticagrelor have shown better pharmacokinetic profiles and efficacy compared to clopidogrel in RCTs.[25-29]

The current evidence of efficacy for newer antiplatelet drugs compared to clopidogrel in PCI is derived primarily from RCTs. Among head-to-head trials, newer P2Y12 inhibitors have shown better efficacy in terms of reduction of stent thrombosis, ischemic events, recurrent MI, and stroke compared to clopidogrel in ACS.,[25,26] Given better pharmacokinetics and greater efficacy reported in these RCTs, guidelines recommend the use of newer P2Y12 inhibitors over clopidogrel.[62] [25] This has resulted in increased utilization of these agents in clinical practice.[63] However, the effectiveness of prasugrel and ticagrelor in ACS patients is not well studied in real-world populations in the United States to see if RCT results translate into standard clinical practice.

The overall objective of study 2 was to compare the effectiveness of newer P2Y12 inhibitors (i.e., ticagrelor and prasugrel) to clopidogrel in a US real-world population.

The specific aims of this study were:

- **Aim 2 (a):** To determine the comparative effectiveness defined as hospitalization due to a composite cardiovascular outcome including recurrent myocardial infarction, unstable angina, recurrent revascularization (Fibrinolysis, PCI, or CABG), stroke (ischemic or hemorrhagic), and heart failure at 30th and 180th-day post PCI across different P2Y12 inhibitors.

- **Aim 2 (b):** To determine if the comparative effectiveness differs across different P2Y12 inhibitors among the patients with STEMI presentation undergoing PCI.
- **Aim 2 (c):** To determine if the comparative effectiveness differs across different P2Y12 inhibitors among the patients with NSTEMI/UA presentation undergoing PCI.
- **Aim 2 (d):** To determine if the comparative effectiveness differs across different P2Y12 inhibitors among the patients with drug-eluting stents placement.
- **Aim 2 (e):** To determine if the comparative effectiveness differs across different P2Y12 inhibitors among the patients with bare-metal stents placement.
- **Aim 2 (f):** To determine if the comparative effectiveness differs across different P2Y12 inhibitors among the male population.
- **Aim 2 (g):** To determine if the comparative effectiveness differs across different P2Y12 inhibitors among the female population.

The results of this study will provide important contributions for the management of ACS by comparing the effectiveness of P2Y12 inhibitors across several important clinical characteristics and examine effectiveness over a shorter period of time than (i.e., 30 and 180 days) than existing RCTs. Current evidence of P2Y12 inhibitor effectiveness in the US populations is limited as most of the observational studies on this topic are conducted outside of the US. This study will address this research gap.

1.3.3. Study 3: Comparative Safety of P2Y12 Inhibitors for Secondary Prophylaxis in Acute Coronary Syndrome after Percutaneous Coronary Intervention

Despite evidence of greater efficacy in RCTs, newer generation P2Y12 inhibitors have also been shown to increase the risk of major bleeding in comparison to clopidogrel. However, observational studies examining bleeding risk between these agents have shown inconsistent results with some indicating higher and others indicating lower risk with newer generation P2Y12 inhibitors compared to clopidogrel.[64-69]

The observational evidence of safety with these drugs comes mostly from registries[30] or electronic healthcare records which may not be generalizable to the entire US population.[64] Thus, there is a need to conduct a study using the data covering a broader US population.

The objective of this study is to study the comparative safety across P2Y12 inhibitors in terms of major bleeding and gastrointestinal bleeding prescribed for recurrent ACS prophylaxis.

The specific aims of this study were:

- **Aim 3 (a):** To determine the comparative safety defined as hospitalization due to a composite serious bleeding outcome including intracranial (IC) bleeding, gastrointestinal (GI), and other serious forms of bleeding referred to as “other bleeding” at 30th and 180th-day post PCI across different P2Y12 inhibitors.

- **Aim 3 (b):** To determine if the comparative safety differs across different P2Y12 inhibitors among the patients at high risk of bleeding.
- **Aim 3 (c):** To determine if the comparative safety differs across different P2Y12 inhibitors among the male population.
- **Aim 3 (d):** To determine if the comparative safety differs across different P2Y12 inhibitors among the female population.
- **Aim 3 (c):** To determine if the comparative safety differs across different P2Y12 inhibitors among the population at advanced age i.e., greater than or equal to 70 years.
- **Aim 3 (d):** To determine if the comparative safety differs across different P2Y12 inhibitors among the population with age less than 70 years.

The results of this study will provide important information related to comparative safety of different P2Y12 inhibitors by studying these in various clinical scenarios. Newer P2Y12 inhibitors reported a higher bleeding risk in RCTs, but their safety is not consistent in observation studies. A balance between the safety and effectiveness of P2Y12 inhibitors is clinically essential. As evidence related to the safety of P2Y12 inhibitors is scarce in the US real-world population, this study will help address the research gap.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

2.1. Background

2.1.1. Acute Coronary Syndrome

CHD is common in the US affecting over 18.2 million Americans[1] and resulting in more than $100 billion indirect costs.[70] Atherosclerosis results in narrowing of coronary arteries which may cause vascular damage and thrombosis,[2] and can cause CHD when there is an inadequate blood supply to meet the myocardium demand. The manifestations of CHD include stable ischemic heart disease, unstable angina, and acute MI.[3] Reperfusion is an essential component of the initial treatment for MI patients to reduce ongoing myocardial damage.[71] Furthermore, patients with established CHD are at increased risk of further vascular events and associated mortality,[4] which makes secondary prevention necessary in long-term management after initial CHD events.[5] CHD is an umbrella term to define coronary artery diseases (CAD); whereas, an acute form of CAD condition is known as an acute coronary syndrome (ACS).

ACS is the life-threatening manifestation of coronary artery disease (CAD) [72] ACS involves an array of clinical presentations involving myocardial infarction and ischemia due to sudden reduction of blood flow in the coronary arteries. The clinical presentation in ACS develops because of the reduced blood flow that is not sufficient to fulfill the metabolic needs of heart muscles. As a result of coronary artery occlusion, ACS results in reversible or irreversible myocardial injury resulting in acute or chronic morbidity and mortality. [10,11]

ACS is presented as:

a) *STEMI:* In STEMI, 100% stenosis (a complete occlusion) takes place resulting in the complete blockage of blood flow in the coronary arteries. This complete blockage lasts for more than 2-4 hours, which is enough for all the myocytes in ventricle walls to die, thus, the full thickness of the ventricle's wall is affected in STEMI. [12] In STEMI, elevated biomarkers i.e., cardiac troponin I (cTnI) and cardiac troponin T (cTnT) in the blood are prognostic and help with confirmation for diagnosis.[73,74]
b) *NSTE-ACS:* Like STEMI, the deprivation of oxygen in the myocardium also takes place in NSTEMI but it doesn't result in the full-thickness necrosis of the myocardium; however, the reduction of oxygen in NSTEMI takes place for enough time to cause damage to the myocardium.[12,13] Based on the elevated biomarkers, NSTEMI-ACS is subdivided into two parts i.e., (i) NSTEMI in which cardiac bio markets are elevated, and (ii) UA in which biomarkers are not elevated.[9]

2.1.2. Pathophysiology of ACS and Role of Platelets in Thrombus Formation

In ACS, the most common cause of disease progression is the narrowing of coronary arteries due to the thrombus formation on atherosclerotic plaque.[75] The formation of these plaques results from the deposition of fatty streaks, endothelial dysfunction, and resulting inflammation. The principal cause of ACS is the rupture of atheromatous plaque or its erosion in the coronary arteries.[76] This plaque rupture exposes the components which are thrombogenic in nature resulting in a clot on top of

the ruptured plaque. This formed clot may cause partial or complete occlusion. The thrombogenic elements of the plaque are further exposed to the blood components in which platelets play a principal role in the formation of thrombus. Further, induction of platelet adhesion and activation takes place because of the exposure of collagen and tissue factors in the blood. This process promotes the release of vasoactive elements, which are derived from platelets including thromboxane A2 (TXA2) and adenosine diphosphate (ADP), which potentiate platelet activation. During platelet activation, conformational changes in the glycoprotein (GP) IIb/IIIa surface receptors of platelets also take place, which further aggregates platelets via fibrinogen bridges. This serves as the final pathway in platelet aggregation and thrombus formation. [75-80]

2.1.3. Disease Epidemiology

Cardiovascular disease accounts for approximately one-third of all global mortality. It is estimated that about 7.5 million global deaths are attributed to CHD.[6] As per a report of AHA/ACC, about 16.5 million US population with age at least 20 years suffers CHD, with a higher prevalence of the disease in males compared to their female counterparts. For example, the total prevalence of CHD in US adults is 6.3% of which 7.4% is male and 5.3% is the female population with at least age of 20 years. It has been reported that the age-adjusted CHD declined in the US from 10.3% in 2001 to 8.0% in 2012.[7]

Among patients with CHD, ACS and sudden death account for most of the mortality related to coronary arteries, resulting in 1.8 million deaths in the US every year. The incidence of ACS has been cited to be increasing with age and occurs approximately 7-10 years sooner in men than in women.[6] The prevalence of MI in US

adults at least 20 years of age is about 3.0%; whereas, angina affects about 3.4% of the population in the same age group.[7]

ACS is common in the US with an annual incidence of approximately 780,000, of which up to 70% is categorized as NSTE-ACS.[9] The percentage of STEMI patients in the US population appears to be decreasing. In a study on 46,086 ACS patients using an integrated healthcare system data, ST-elevation hospitalizations decreased from 47.0% in 1999 to 22.9% in 2008.[7] There is also evidence of an increasing number of patients with NSTEMI in the US. For example, a study from the National Registry of Myocardial Infarction which reviewed over 2.5 million MI patients reported a significant increase in the NSTEMI ACS presentation from 19% to 59% from the year 1994 to 2006.[81] In the US, NSTE-ACS affects more than 625,000 patients every year which accounts for almost three fourth of all the patients suffering ACS.[82]

Although the incidence of MI, in general, is declining in the US over time, the mortality rate continues to be alarming. It has been reported that about half of the patients suffering from an acute MI attack die before even reaching the hospital. However, the in-hospital mortality rate has decreased over the last decade and is reported to be about 5%. The one-year mortality after an acute MI attack is indicated to be about 15%.[83] It is important to note that there is a differential risk of mortality with time-based on ACS presentation. For example, a pooled analysis which compared the risk of death over 2 years of follow-up, demonstrated that the risk of death among patients with STEMI was greatest within the first 30 days of percutaneous coronary intervention. However, those suffering NSTEMI-ACS were at increased risk of death during the entire study period of 2 years.[84]

Additionally, recurrent ACS in the US is worrisome indicating possible treatment failures. The 2021 update of heart disease and stroke statistics[85] suggested that about 720,000 Americans will have a new ACS event annually with approximately 335,000 of these events being categorized as recurrent. This recurrent pattern of ACS needs attention and should be studied well for the better management of ACS to reduce the recurrence of these events in the US.

2.1.4. Cost of Acute Coronary Syndrome

Hospitalization for Acute MI is amongst the top 5 most expensive conditions in the United States. It was indicated as the fourth most expensive condition in a report from the Agency for Healthcare Research and Quality (AHRQ).[86] The financial impact of ACS is exceedingly high on the American healthcare system as it is associated with more than $150 billion every year in terms of direct medical expenditure.[87] As an estimate, about 20% of the patients are readmitted to the hospital within one year of the initial hospitalization accounting for 60% of the overall ACS cost related to rehospitalizations only.[88,89] The cost of PCI procedures in ACS patients is overwhelming as it is one of the most commonly performed medical procedures in the hospital setting with an estimated cost burden of $25 billion every year to the healthcare system.[90] Additionally, recurrent ACS within 30 days following PCI has been cited as a significant predictor of the ACS-related cost. In a study, that identified PCI cases from 722 US hospitals using the data from The Healthcare Cost and Utilization Project National Readmission Database, readmission within 30 days increased the cumulative cost by 45%.[91]

2.1.5. Initial Management of Acute Coronary Syndrome

2.1.5.1. STEMI

MI is a pathological condition accompanied by myocardial ischemia in which there is evidence of myocardial injury. MI is diagnosed with an increased level of troponin along with the typical supportive patient's symptoms. Diagnosis is principally supported with the electrocardiographic (EKG) changes suggesting ST wave elevated or a new loss of viable myocardium evident from cardiac imaging. [92]

Once a patient is diagnosed with an acute STEMI, the early management involves mainly relieving the ischemic pain, assessment of patient's hemodynamic state and correction of any abnormality assessed, instigation of reperfusion therapy principally with PCI or fibrinolysis (if PCI not available/possible). Patients undergoing treatment for STEMI are also prescribed beta-blockers to prevent ventricular arrhythmias and antithrombic therapy to prevent restenosis while in the hospital setting. At the same time, patients are initiated with antiplatelet drugs, angiotensin-converting enzyme inhibitors, statins, and anticoagulation to improve their long-term prognosis. [93]

Recommendation on Reperfusion in STEMI

a) PCI:

PCI refers to a revascularization procedure with stenting or non-stent procedure such as atherectomy and/or balloon angioplasty on affected coronary arteries. For PCIs, stenting is the standard of care,[94] and the ACC/AHA recommends that in STEMI patients, primary PCI should be performed within 12 hours of symptom onset.[42] However, for those patients who are presented in the hospital setting 12 to 24 hours of

symptom onset, primary PCI is suggested if the patient is not hemodynamically stable or has severe symptoms of heart failure.[93] Overall, primary PCI is the recommended method of reperfusion in STEMI patients when it can be done in a timely fashion.[42]

ACC/AHA guidelines recommend either a BMS or DES among STEMI patients undergoing primary PCI. [42] The use of second-generation DES is believed to be a gold standard and is recommended to be used over BMS for primary PCI in STEMI patients because of better efficacy.[95] For example, an RCT that compared the long-term effect of BMS versus DES showed that the repeated revascularizations and restenosis were significantly lower with the use of DES.[54] Furthermore, in an observational study using Medicare data, DES use was associated with a 28% and 19% reduced risk of death and MI as compared to BMS suggesting better effectiveness of DES in a real-world population.[96]

Additionally, in an expert review, the use of second-generation DES is indicated to be associated with better clinical outcomes immediately following a PCI as well as long-term benefit compared to BMS. The use of second-generation DES was also indicated to be a cost-effective choice compared to BMS or first-generation DES. The use of first-generation DES is now uncommon in the United States due to the superiority of second-generation stents.[94,97]

b) Fibrinolysis

The use of fibrinolytic therapy is also recommended by the 2013 ACC/AHA guideline for the management of STEMI. However, as per the guidelines, the use of fibrinolysis should be used only if the PCI cannot be performed within 120 minutes of the patient's first medical contact. The use of fibrinolysis is recommended within 12 hours of

symptoms onset; nevertheless, it may be considered up to 24 hours if the patient has ongoing anginal pain and the PCI is not available.[93]

It should be noted that in an RCT, fibrinolysis was effective for reperfusion if it was followed with a PCI in a timely fashion; but, it caused higher intracranial bleeding when compared to primary PCI.[98] Thus, primary PCI is advocated to be the recommended strategy among patients presented with a STEMI.[99]

2.1.5.2. NSTEMI/UA

Contrary to STEMI, in NSTEMI, there is an absence of ST elevation in EKG suggesting an NSTE-ACS event. As previously stated, NSTE-ACS is subdivided into NSTEMI and UA. In NSTEMI patients, there is an elevation of cardiac bio-markets suggesting necrosis along with patients' symptoms suggestive of myocardial ischemia. On the other hand, if the cardiac biomarkers are not elevated it is termed UA. In NSTEMI presentation, EKG pattern may also indicate ST wave depression or a prominent T-wave. Thus, NSTEMI and UA are closely related but differ in severity in the sense that in NSTEMI presentation, there is an injury to the myocardium.[100,101]

The early management of patients presenting with NSTEMI and UA is similar to STEMI management; however, fibrinolysis is not recommended in these patients (different from STEMI). There is no evidence of any benefit with fibrinolysis in NSTEMI and UA patients.[102] Additionally, among the NSTE-ACS patients fibrinolysis is evident to cause intracranial hemorrhage and MI. Thus, the 2014 AHA/ACC guideline for the management of patients with NSTEMI doesn’t recommend fibrinolysis among the patients presented with NSTEMI.[82,100] In NSTE-ACS, like STEMI, an early invasive strategy with an intention to revascularize the patient within 48 hours of symptom onset

is recommended for high-risk patients by the current ACC/AHA guidelines[43] Like STEMI, the use of DES over BMS is also recommended in NSTE-ACS patients as DES has been reported to be linked with better outcomes. For example, in an RCT studying NSTEMI patients, restenosis in the DES group was significantly lower compared to the BMS group over a follow-up of 9 months. Additionally, at 2 years of follow-up, target vessel revascularization incidence was lower in the DES group.[103] Thus, like in STEMI patients, evidence suggests the use of DES over BMS in NSTEMI as well.

2.2. Literature Review

2.2.1. Long Term Prophylaxis/Management with Dual Antiplatelet Therapy (DAPT) Following Initial Management

Platelet inhibition serves a central role in the prophylaxis of recurrent atherothrombotic events among patients with coronary heart disease. Oral antiplatelet therapy includes a DAPT which includes a combination of aspirin for cyclo-oxygenase-1 inhibition along with the platelet adenosine diphosphate P2Y12 receptor inhibition by either clopidogrel, prasugrel, or ticagrelor. DAPT involving aspirin and clopidogrel has been studied well across different arrays of CAD, whereas newer generation P2Y12 inhibitors i.e., prasugrel and ticagrelor are evaluated in ACS patients.[5,104]

Newer generation P2Y12 inhibitors i.e., prasugrel and ticagrelor cause potent inhibition of the P2Y12 receptor and are reported to achieve maximum platelet inhibition in healthy volunteers within an hour of the loading dose. Nevertheless, among the ACS patients in a real-world setting following a PCI, these drugs are associated with different pharmacokinetics especially in STEMI and NSTE-ACS. This difference may have an important implication for the utilization of these newer agents following a primary PCI.[105]

a) The emergence of Clopidogrel as a Gold Standard Antiplatelet Therapy Post Revascularization with Stent Placement

In a landmark RCT in 1996, dual antiplatelet drug therapy that included a combination of aspirin with ticlopidine resulted in a superior efficacy compared to anticoagulant therapy for secondary prophylaxis. In this trial, DAPT with aspirin and ticlopidine reduced the incidence of recurrent cardiac events significantly compared to anticoagulant therapy along with reduced hemorrhagic events.[106] This trial shifted the focus to antiplatelet drugs instead of anticoagulation post stent placement in the coronary artery for secondary prophylaxis. As a result, in the year 1999, DAPT with ticlopidine and aspirin became a gold standard following a PCI.[107]

Although effective, DAPT involving ticlopidine was associated with life-threatening adverse reactions such as bone marrow aplasia, neutropenia, thrombocytopenia, and cholestasis.[108,109] Thus, safety was a major concern with utilization of DAPT involving ticlopidine post stent implantation. Later, in 1999, another RCT showed a better safety profile of clopidogrel that also belonged to the same class of antiplatelet inhibition as ticlopidine i.e., P2Y12 inhibitors. This trial introduced clopidogrel as a better alternative to ticlopidine with a simpler dosing regimen as well.[16] Following the year 1999, various RCTs comparing clopidogrel with ticlopidine showed and documented the advantage of clopidogrel. For example, in the CLASSICS trial (2000), clopidogrel significantly reduced the risk of major peripheral or bleeding complications, neutropenia, thrombocytopenia compared to ticlopidine after stent placement.[17] Later, in 2001, another trial proved better tolerability of clopidogrel compared to ticlopidine as a significantly lower number of patients in clopidogrel (1.62%) failed to complete the

therapy of 2-week regiment compared to ticlopidine (3.64%) in this trial.[18] Additionally, in 2002, a meta-analysis of RCTs and registry including 13,955 patients reported a significant 28% and 45% lower odds of ischemic events and mortality associated with clopidogrel compared to ticlopidine, respectively.[110] Thus, based on the evidence from various RCTs the use of clopidogrel after stent placement is associated with a better clinical outcome compared to ticlopidine, and hence became the gold standard for secondary prophylaxis post-PCI.[111]

b) Potential Problems with Clopidogrel Based DAPT Regimen

Because clopidogrel is a prodrug, it needs biotransformation in the body by iso-enzymes in the liver. Although DAPT involving clopidogrel is effective in reducing major adverse cardiac outcomes, its clinical application is hampered by pharmacodynamic characteristics resulting in a slower onset of action and variable response that may increase the risk of stent thrombosis and recurrent myocardial infarction.[20] As per a report at least 10% of cardiovascular events reoccur within one year of ACS event, which is worrisome.[14]

Additionally, DAPT involving clopidogrel is reported to have high post-treatment reactivity and treatment resistance that may potentially cause a stent thrombosis after a PCI involving a stent insertion.[22,23] For example, in a prospective cohort study involving PCI patients with DES stents, no responsiveness to DAPT with clopidogrel was labeled as a strong predictor of stent thrombosis.[112] Furthermore, in an RCT, up to 25% of the STEMI patients managed with primary PCI with stenting were resistant to clopidogrel posing a significant risk of recurrent cardiovascular events.[24]

Another major problem with the clopidogrel-based DAPT regimen is inter-subject variability in platelet inhibition.[113] Differences in individual ability to metabolize clopidogrel to its active compounds have been cited as a plausible mechanism in the variability in platelet inhibition.[21] As clopidogrel is metabolized to its active metabolite by CYP2C19, genetic variation has been indicated to be linked with variation in platelet inhibition.[114] Thus, alternative pharmacological strategies and the evaluation of more intensive and consistent antiplatelet therapy with newer P2Y12 inhibitors (i.e., prasugrel and ticagrelor) compared with clopidogrel have been advocated.[113,115] Despite the limitations of its use, clopidogrel-based DAPT is the most widely prescribed regimen as evident by various observational studies conducted in many countries.[116]

c) Evidence of Safety and Efficacy Related to Newer Antiplatelet Agents Compared to Clopidogrel Post PCI

The difference in terms of efficacy/effectiveness and safety has been observed in RCTs and observational studies comparing these medications which are discussed below:

i. Clopidogrel vs Prasugrel

Prasugrel is a thienopyridine derivative that acts with a mechanism similar to clopidogrel. It was approved by US Food and Drug Administration (FDA) in 2009 to prevent recurrent cardiovascular events following a PCI in ACS patients.[117] Prasugrel has been compared with clopidogrel in various RCTs and observational studies in a process to optimize antiplatelet therapy for secondary prophylaxis of ACS. The most important RCTs and observational studies are described below.

- **Randomized Controlled Trials:** In a major RCT, TRITON-TIMI 38, which recruited 13,608 patients with all spectra of ACS i.e., STEMI, NSTEMI & UA with planned PCI, prasugrel therapy resulted in a statistically significant 27% reduction in the primary efficacy endpoint (composite of cardiovascular mortality, nonfatal MI and stroke) compared to clopidogrel, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality in this trial did not differ between prasugrel and clopidogrel groups at a follow-up time of 14.5 months.[118] Additionally, prasugrel in another RCT was more effective and had similar safety compared to clopidogrel when it was studied only in STEMI patients.[119] Furthermore, another trial studying only NSTE-ACS also reported a similar efficacy in terms of cardiovascular death, MI, and stroke and a similar risk of bleeding.[120] Overall, the evidence related to the efficacy and safety of prasugrel and clopidogrel in controlled conditions appears to be inconsistent.

- **Observational Studies:** Observational evidence comparing prasugrel and clopidogrel has produced mixed evidence with very limited studies conducted in the US In a pilot study, prasugrel (n=85) was not associated with better effectiveness and safety compared to clopidogrel (n=136).[121] Also, in another US-based prospective cohort study that included 19,914 patients undergoing PCI from 8 centers from the year 2010 to 2013, there was no difference between major adverse cardiac outcomes and bleeding between prasugrel and clopidogrel.[30] However, in a Swedish study, among patients with ACS undergoing PCI, prasugrel was found to be associated with better effectiveness compared to clopidogrel in terms of reduction of the composite of in-hospital mortality, recurrent MI, and stroke (3.0% vs 4.3%;

p=0.02). However, bleeding events were more frequent in the prasugrel group (4.1% vs 3.0%; p=0.048) in this propensity score-matched analysis.[122] Furthermore, in an Australian study, there was no difference in unadjusted 30-day mortality, MI, or MACE between prasugrel and clopidogrel. Also, there was no difference in in-hospital bleeding as well.[31] Thus, among observational studies, there are reported mixed results related to the safety and effectiveness of prasugrel compared to clopidogrel.

The evidence related to efficacy/effectiveness and safety of prasugrel and clopidogrel from RCTs and observational studies is inconsistent. Currently, there are a lack of studies comparing prasugrel with clopidogrel in real-world populations with one study[30] comparing these drugs prospectively using data from 8 hospitals that may not be generalizable to a broader US population. Thus, there is a need of a study comparing the effectiveness and safety of these drugs in the US population using data that can better represent the US population.

ii. Clopidogrel vs Ticagrelor:

Ticagrelor was approved in 2011 by the FDA for its use in ACS patients to prevent recurrent adverse cardiac outcomes.[123] Ticagrelor, unlike clopidogrel and prasugrel, does not require biotransformation in the liver and offers direct-acting P2Y12 receptor inhibition. Also, it reversibly binds to P2Y12 receptors to block platelet activation differently than thienopyridines that bind irreversibly.[14] Ticagrelor has been compared with clopidogrel as the standard of care in RCTs and observational studies for use in the secondary prevention of ACS.

- **Randomized Controlled Trials:** In a multicentered RCT (PLATO), that recruited 18,624 patients hospitalized irrespective of ACS presentation, ticagrelor significantly reduced the risk of major adverse cardiovascular outcomes by 16% compared to clopidogrel in a follow-up time of 12 months. In this trial, ticagrelor was also not associated with an increased risk of overall major bleeding compared to clopidogrel (11.6% and 11.2%; p=0.43). However, the use of ticagrelor resulted in fatal intracranial bleeding and major bleeding not related to coronary artery bypass grafting.[26,27] Also, in a subgroup analysis of the PLATO trial, ticagrelor was linked to a reduced risk of stent thrombosis and this benefit was robust across stent type and treatment characteristics.[28] It should be noted that in the PLATO trial, there was no difference in terms of outcomes in the North American population as there was a significant interaction with the region. The absence of a difference is hypothesized to result from high doses of aspirin used in the North American region compared to the rest of the world.[124,125] However, in an RCT that was conducted in East Asia (Japan, South Korea, and Taiwan), ticagrelor was not statistically significantly different compared to clopidogrel in terms of major adverse cardiac outcomes and major bleeding.[126] Another RCT conducted in China on 400 STEMI patients resulted in better efficacy of ticagrelor compared to clopidogrel but both groups were not different for safety outcomes.[127] Thus, RCTs comparing ticagrelor and clopidogrel reported mixed results as far as the efficacy and safety of these agents were concerned.

- **Observational Studies:** Evidence of safety and effectiveness of ticagrelor compared to clopidogrel comes from different parts of the world. In a real-world analysis

including 9,684 ACS patients from the Korean Acute Myocardial Infarction Registry, following PCI, ticagrelor was associated with better clinical outcome in terms of major adverse cardiac outcomes (5.6% vs 9.2%; p=0.001). However, it was associated with significantly higher in-hospital bleeding compared to clopidogrel.[33] Additionally, a prospective multicenter cohort study based on GReek AntiPlatElet (GRAPE) Registry followed 2047 ACS patients for a year to assess comparative effectiveness and safety. In this study, ticagrelor was similar to clopidogrel (HR: 0.78; 95% CI (0.5-1.12)) for the major adverse cardiovascular outcome. Also, more frequent bleeding was observed with ticagrelor compared to clopidogrel (HR: 1.81; 95% CI, 1.55-2.10).[35]

More recently, two more studies have been reported studying patients from the North American region (i.e., Canada and United States). In the first study conducted in Canada,[65] researchers followed 11,185 ACS patients undergoing PCI for one year using data from the Alberta Provincial Project for Outcome Assessment in the Coronary Heart Disease registry. Ticagrelor was not associated with better outcomes in terms of major adverse cardiac events in this study compared to clopidogrel (adjusted hazard ratio: 0.97; 95% CI, 0.85-1.10). Additionally, ticagrelor was associated with a higher risk of dyspnea and major bleeding. In the second study conducted using two different electronic health records from the United States,[64] researchers reported mixed results. Analysis including IQVIA hospital data (first EHR data) in this study showed no difference between ticagrelor and clopidogrel (HR: 1.06; 95% CI (0.90-1.24); p= 0.52) for the net adverse clinical events (NACE). However, when the analysis was performed using electronic health records from OPTUM), ticagrelor was associated with a higher incidence of NACE

compared to clopidogrel (HR: 1.08; (95% CI (1.00-1.17); p= .05). Nevertheless, the pooled analysis showed both groups to be similar in the risk of NACE. It should be noted that the pooled analysis in this study also included the data from South Korean nationwide database. These studies are important in the sense that the PLATO trial underrepresented the North American population and there was a significant interaction with region that suggested the North American population was not benefited by ticagrelor. Thus, there is a need for a comprehensive study comparing these agents in the United States to measure the magnitude of the difference in safety and effectiveness with these agents in the US population.

The evidence related to efficacy/effectiveness and safety from RCTs and observational studies is inconsistent comparing ticagrelor and clopidogrel. It is important to note that the PLATO trial showed a regional interaction and the US population was not benefited by ticagrelor in this trial. Additionally, studies in the real-world setting in the US used EHR and registry data that may not be generalizable to the US population. Thus, there is a need for a comprehensive study conducted using real-world data representing the broader US population.

iii. Ticagrelor vs Prasugrel:

It is evident from various studies that newer P2Y12 inhibitors are potent and provide greater platelet inhibition. Current AHA/ACC guidelines recommend using ticagrelor and prasugrel which are based on the results of RCTs in which both of these drugs were compared with clopidogrel. Although newer P2Y12 inhibitors (i.e., prasugrel and ticagrelor) are used in clinical practice in the US, there is very limited evidence that compares both of these drugs head-to-head in the US population. This lack of evidence

may serve as a source of confusion while deciding whether to select prasugrel or ticagrelor if greater platelet inhibition is desired. Following are the studies that have been conducted comparing prasugrel and ticagrelor:

- **Randomized controlled trials:** Recently in 2019, the first RCT (ISAR-REACT 5 trial) compared prasugrel and ticagrelor head-to-head among the patients suffering ACS and reported a higher incidence of MI, stroke, and death as a composite outcome with ticagrelor compared to prasugrel (HR:1.36; 95% CI (1.09-1.70)) over one year. The risk of major bleeding was found to be similar in both groups (HR: 1.12; 95% CI (0.83-1.51)).[128] However, this RCT did not include patients from the US as it included ACS patients from 21 centers in Germany and 2 centers in Italy. Before ISAR-REACT 5 trial, PRAGUE 18 study,[129] an open-label Phase IV controlled clinical trial, recruited ACS patients from 14 cardiology centers in Czech Republic to study ticagrelor with prasugrel reported no difference between the primary endpoint that included composite of re-infarction, stroke, serious bleeding, target vessel revascularization, and all-cause mortality within 7 days of randomization (OR: 0.98; 95% CI (0.55-1.73)). Importantly, this study was discontinued prematurely for futility. It is important to note that none of the patients in these studies was included from the US population.

- **Observational studies:** The evidence related to observational studies also comes from different parts of the world. In a retrospective cohort study that included ACS patients from 11 University hospitals in 6 different countries in Europe,[130] prasugrel was found to be associated with better outcomes in the reduction of major adverse cardiac outcomes (5% vs 8.1%; p=0.001) and net adverse clinical events (5.3% vs

8.5%; p=0.001) compared to ticagrelor. Also, bleeding events were observed lower in the prasugrel group (1.5% vs 4.0%; p=0.01).

Few studies have compared prasugrel with ticagrelor in the real-world US population. In a retrospective study[131] conducted using data from IMS Health Hospital Charge Data Master (2011-2013), among the ACS patients undergoing PCI, prasugrel was associated with 22% lower net adverse clinical effect compared to ticagrelor (RR: 0.78; 95% CI (0.64-0.94)). Also, major adverse cardiac events (RR: 0.80; 95% CI (0.64-0.98)) and major bleeding (RR: 0.65; 95% CI (0.45-0.95)) was also observed less in prasugrel treated patients compared to those treated with ticagrelor. Similar results were reported in another study that used data from ProMetis Lx claims data (2011-2013) in the US among the patients undergoing a PCI.[132] In this study the net adverse clinical effect (15.7% vs 18.0%; p=0.009) and major adverse cardiac events (14.4% vs 16.4%; p=0.02) were in favor of prasugrel compared to ticagrelor. Of note, a study by Dawwas et al.,[133] using MarketScan claims data (2011-2016) that included overall ACS patients reported better outcome with ticagrelor compared to prasugrel in the reduction of recurrent CVD event as a composite of MI and stroke (HR: 0.80; 95% CI (0.70-0.92)) and major bleeding (HR: 0.54; 95% CI (0.41-0.70)). It should be noted that this study included patients with all spectrum of ACS without looking at whether these patients underwent revascularization (by PCI, CABG, or fibrinolysis) or not (managed with medical therapy alone). This is important to note that treatment guidelines by AHA/ACC differ based on how initially ACS events are managed.

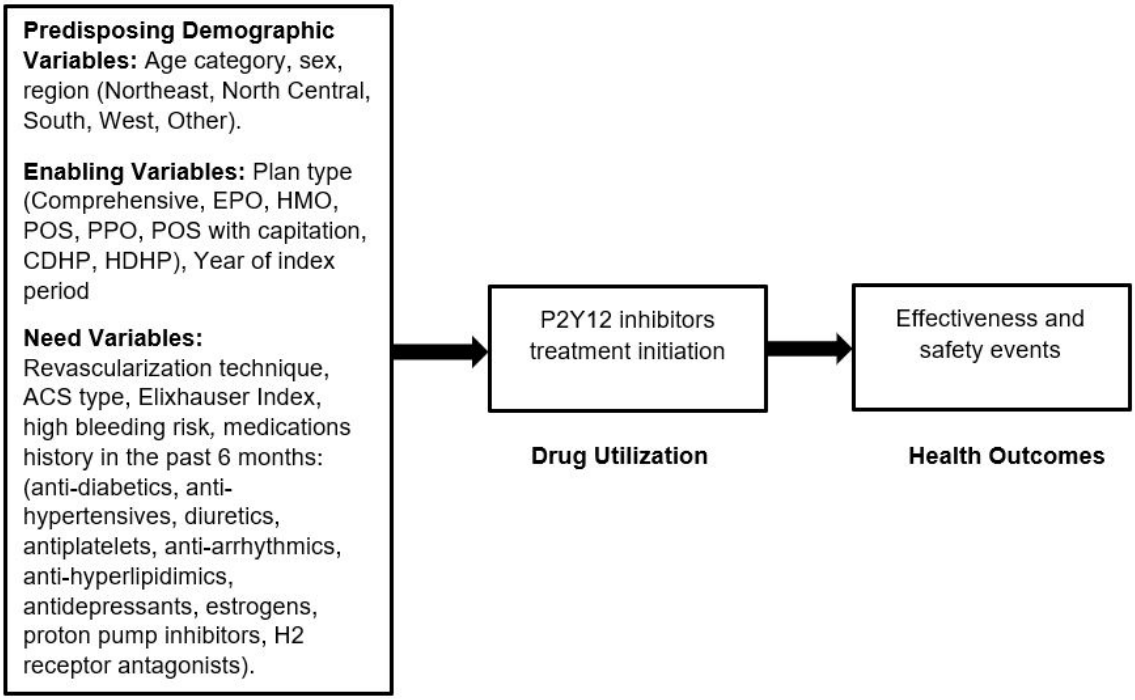
Thus, there is mixed evidence related to comparative effectiveness between ticagrelor and prasugrel in the US population with no randomized comparison. The

observational studies which included ACS patients undergoing a PCI may not be generalized to a broader US population; whereas the study by Dawwas et al., which studied ACS patients didn't specifically include patients undergoing a PCI. Thus, it is imperative to study the ACS patients undergoing a PCI comparing ticagrelor and prasugrel using a data sample that can represent the US population undergoing a PCI.

2.2.2. Conceptual Framework: Andersen's Behavior Model

A conceptual model may aid to determine the appropriate variables for a research study. In this dissertation, Andersen's Behavior Model (ABM) of Health Services Use[134] was employed to select confounder variables. Andersen's Behavioral Model of health services was originally proposed in the 1960s. The core principle of ABM is that the utilization of health services is affected by patient characteristics, which can be divided into three main components: 1) predisposition to the use of services, 2) factor which enables or impedes service utilization; and 3) the need for care.

Figure 2. 1 Andersen's Behavioral Model of Health Service Use



Source: Andersen's behavioral model of health service use (1995)[134]

Based on ABM, we selected the following variables:

a) **Predisposing variables** in this study included age, gender, and geographical region. We considered patients' age as a potential predisposing factor because older age is associated with increased bleeding risk.[135] As newer P2Y12 inhibitors are associated with a high risk of major bleeding compared to clopidogrel, clinicians might choose safer antiplatelet drugs in older patients which may result in a differential pattern of prescribing. Literature suggests a significant state-level variation in cardiovascular health in the US.[136] These differences in cardiovascular health may affect the prescription of P2Y12 inhibitors which will be explored in this study. Furthermore, female sex has been shown to have increased bleeding risk which could incline clinicians towards safer antiplatelet drug prescription, thus, we used gender as a predisposing demographic variable in this study.
b) **Enabling characteristics** potentially render or impede the use of healthcare services. This set of variables in our study comprised of the type of insurance plan/coverage, and the year of the index date. We considered a type of insurance plan as an enabling variable because variation in the prescription drug coverage may influence the patient's and physician's choices of treatment depending on whether a specific plan covers the choice of drug.[137] With time the adoption of newer P2Y12 inhibitors is seen in the clinical practice post-FDA approval of these drugs. As the availability of newer medications with time may enable the physicians to choose from the available P2Y12 inhibitors as per the patient's characteristics, we used the index year of antiplatelet drug use as an enabling variable.

c) Finally, we included several **need variables** in our model which may represent both the perceived and actual health condition of a patient that mandates the utilization of healthcare services. We included mode of revascularization, type of stents, type of ACS presentation, prior comorbidities in the form of the Elixhauser comorbidity index (EI) for readmission, high bleeding risk, and medication history in the past six months.

We included the mode of revascularization as our need variable because the technique may vary depending on the patients' need for a particular revascularization method. For example, high-risk patients with multiple diagnoses of infarct in a single coronary artery may require CABG compared to PCI; whereas, PCI may be sufficient to revascularize a culprit artery. However, in the scarcity of the facility to perform a CABG or PCI, patients may be in immediate need of a fibrinolytic therapy on presentation in an ER. Given that the need for treatment with P2Y12 inhibitors varies with revascularization technique, we opted for the mode of revascularization as a need variable.

We considered the type of stent as another need variable because current guidelines for antiplatelet therapy vary depending on whether bare-metal stent (BMS) or drug-eluting stent (DES) is used in PCI. For BMS current guidelines recommends treatment with antiplatelet medications for at least one month; whereas, for DES, the recommendations are to prescribe medications for 6-12 months.[138] The need for long-term treatment with newer P2Y12 inhibitors can be expensive because of the unavailability of generic versions, which may cause a substantial burden of out-of-pocket

payment on the patients. Thus, the cost of treatment depending on the type of stent may affect the clinicians' decision for the P2Y12 prescription.

Furthermore, we included the type of ACS presentation whether STEMI or NSTEMI/UA as a need variable because STEMI is an emergency situation, which requires immediate treatment, and the course of treatment can be different compared to NSTEMI/UA. STEMI patients are younger compared to NSTEMI[139] which may incline clinicians towards the use of newer P2Y12 inhibitors. Additionally, newer P2Y12 inhibitors are potent and have superior efficacy in STEMI patients compared to clopidogrel.[140] This may cause a discrepancy in the prescription of P2Y12 inhibitors. We differentiated STEMI and NSTEMI patients using validated and published ICD 9 and 10 codes with high sensitivity.[141-143]

Previous comorbid conditions may cause a variation in the decision to prescribe different P2Y12 inhibitors among patients with coronary heart disease. Studies have reported increased use of newer P2Y12 inhibitors and better clinical outcomes in terms of major cardiac events among the patients with fewer comorbidities; whereas increased use of clopidogrel has been reported among patients with more comorbidities.[144,145] These factors may influence the prescribing of these agents as well. To guide the comorbidities as a need variable in our model, we utilized the EI index. We categorized the EI index into five different categories based on EI scores: (i) EI < 0 as category 0, (ii) EI=0 as category 1, (iii) EI=1 to 5 as category 2, (iv) EI= 6-13 as category 3, and (iv) EI >=14 as category 4 as previously published and tested in coronary heart disease.[146] All ICD codes to identify Elixhauser conditions were taken from *Elixhauser Comorbidity Software, Version 3.7*.[147]

Bleeding risk with P2Y12 inhibitors is a serious concern, and newer P2Y12 inhibitors are associated with increased bleeding risk in the RCTs and a meta-analysis.[148] This association may cause clinicians to choose clopidogrel over newer P2Y12 inhibitors among those who are at increased risk of major bleeding. We used AHA guidelines [41]to identify high bleeding risk population. We used any history of high-risk comorbid conditions (i.e., diabetes, anemia, chronic kidney disease, low body weight), any major bleeding (i.e., intracranial, gastrointestinal, and any other major bleeding) in the last 6 months to determine if patients were at increased risk of major bleeding. We also included any concomitant use of the medication linked to higher bleeding risk i.e., oral anticoagulants, prescription non-steroidal anti-inflammatory drugs (NSAIDs), or corticosteroids as an additional bleeding risk as per AHA recommendations.

Finally, we also considered the history of medications in the past 6 months. We considered the use of anticoagulants, antiplatelet drugs, antiarrhythmic drugs, antihypertensives, antidiabetics, diuretics, antacids based on the studies published previously.[64,133,149,150] We included antidepressant therapy as a need variable because of the association of antidepressants with increased risk of MI.[151,152] This increased risk of MI may require a higher need for aggressive antiplatelet therapy which may cause a physician to prescribe newer antiplatelet drugs compared to clopidogrel. Additionally, we further included estrogen as its use is associated with an increased risk of thrombosis[153] which might need aggressive antiplatelet therapy as well.

The ABM model **(Figure 2.1)** suggests that the initiation of P2Y12 inhibitors may be influences by predisposing patient characteristics, enabling factors, and patient health

needs. Examining prescribing of different agents across these factors is important. In addition, these factors may act as potential confounders which should be controlled for during comparative effectiveness and safety evaluations of P2Y12 inhibitors.

SUMMARY

ACC/AHA guidelines for the selection of P2Y12 inhibitors differ by clinical characteristics and the type of revascularization employed to restore blood in the coronary arteries. Specifically, current recommendations caution the use of P2Y12 inhibitors in high-risk population such as among patients at high bleeding risk, with stroke history, and at an advanced age. Although these guidelines differ across different patient groups, there is currently limited information about the adoption of these clinical guidelines across these different patient populations in a real-world population of US patients.

Although RCTs have been conducted to compare the safety and efficacy of different P2Y12 inhibitors, the results of these studies are inconsistent. In addition, observational evidence of comparative effectiveness and safety is limited in the US and has not adequately examined the impact of different clinical characteristics on these outcomes. These gaps in the literature are addressed in this dissertation through the completion of the following studies.

CHAPTER 3: STUDY 1

PRESCRIPTION PATTERNS OF P2Y12 INHIBITORS FOLLOWING REVASCULARIZATION IN THE UNITED STATES: 2013-2018

3.1. Introduction

Coronary heart disease (CHD) is common in the US affecting over 18.2 million Americans and resulting in more than $100 billion in indirect costs.[70] Atherosclerosis results in narrowing of coronary arteries which may cause vascular damage and thrombosis,[2] and can cause CHD when there is an inadequate blood supply to meet the myocardial demand. The manifestations of CHD include stable ischemic heart disease, unstable angina, and acute myocardial infarction (MI).[3] Reperfusion is an essential component of the initial treatment for MI patients to reduce ongoing myocardial damage.[71] Furthermore, patients with established CHD are at increased risk of further vascular events and associated mortality,[4] thus secondary prevention necessary after initial CHD events.[5]

The American Heart Association (AHA) strongly recommends secondary prophylaxis with a P2Y12 inhibitor and aspirin, widely known as dual antiplatelet therapy (DAPT).[60] P2Y12 inhibitors utilized for secondary CHD prophylaxis include clopidogrel which was approved by the US FDA in 1997 as well as the newer agents prasugrel and ticagrelor which were approved by the FDA in 2009 and 2011,[61] respectively. Compared with clopidogrel, these newer agents have more potent and predictable antiplatelet aggregation profiles, attributed to consistent pharmacokinetics and dynamics.[25] However, the AHA guidelines on the type of P2Y12 agent to prescribe differ with (i) patient's clinical characteristics (e.g., high bleeding risk and history of stroke), and (ii) the

type of revascularization technique (percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or fibrinolysis).[41] The approval of newer P2Y21 inhibitors has led to their utilization in clinical practice.[154,155] However, currently, there are no studies that have differentiated real-world prescribing patterns following different revascularization procedures and clinical characteristics.

Given their better pharmacokinetic profile, the use of newer P2Y12 inhibitors is recommended under clinical practice guidelines, if not contraindicated for individual patients.[62] However, evidence suggests that clopidogrel may be a safer option among elderly patients and those at a high risk of bleeding and a history of stroke.[135] Little information is currently available describing the adoption of newer P2Y12 inhibitors in real-world populations. The main objective of this study is to examine differences in the prescribing of P2Y12 agents across important clinical characteristics such as high bleeding risk and the type of revascularization used, and also to determine the predictors of utilization of one P2Y12 inhibitor over the other.

3.2. Methods

Data Source

This study was done using the IBM MarketScan® databases from January 1st, 2013 to December 31st, 2018. The Commercial Claims and Encounters (CCAE) database includes information on more than 30 million commercially insured beneficiaries and the Medicare Supplemental and Coordination of Benefits (MDCR) data includes information on more than one million Medicare beneficiaries with supplemental benefits. CCAE sample in our study included patients aged 18 to 65 years; whereas MDCR samples included patients ≥65 years. These databases include enrollment information, inpatient and outpatient medical claims and outpatient pharmacy claims. CCAE data contains information on healthcare coverage and service use of individuals under a variety of different insurance offerings including fee-for-service (FFS), capitated, preferred provider organization (PPO), health maintenance organization (HMO), and others. Whereas MDCR database contains information of Medicare-eligible employees who have additional coverage through supplemental plans or employers. Similar to CCAE files, the MDCR database also contains information on healthcare coverage and service use of individuals under a variety of plan offerings.

Patient Inclusion and Exclusion

We included patients discharged from the hospital with a primary diagnosis of CHD. CHD events were identified using ICD-9 & 10-CM codes **(Appendix Table 3.1)**.[70] Included patients had continuous enrollment for ≥ 6 months in a health plan with medical and pharmacy benefits. Included patients had a diagnosis of CHD and initiated

clopidogrel, prasugrel, or ticagrelor within 14 days of revascularization after a CHD event.

Drug claims were identified by National Drug Code (NDC) from outpatient pharmacy claims data using prescription fill date. We employed the intention to treat (ITT) approach,[156] using the first prescription fill as the index dispensing of P2Y12 inhibitor. Once identified, patients were retained in the initial drug category for the entire study period.

Revascularization methods included fibrinolytic therapy, CABG, and PCI. We considered only the first revascularization event with a P2Y12 inhibitor. Patients with multiple revascularization procedures during a single admission, were categorized by the most invasive procedure (e.g. patients experiencing both PCI and fibrinolytic therapy were categorized as PCI, those having both PCI and CABG were categorized as CABG).[157-160] The revascularization procedures were determined using Current Procedure Terminology (CPT) codes and the Healthcare Common Procedure Coding System (HCPCS), and ICD 9 and 10 procedure codes published previously[69,161-164] **(Supplementary Material: Appendix Table 3.1)**.

Study Design

We used a cross-sectional study design to determine prescription patterns of P2Y12 inhibitors across patients' characteristics and type of revascularization procedure used in CHD patients from January 1st, 2013 to December 31st, 2018.

Description of prescription patterns of different P2Y12 inhibitors for the full study period: Predictors of drug selection were determined in the overall patient cohort (2013-

2018) based on variables grouped using Andersen's Behavior Model (ABM) of Health Services Use[134] **(Figure 2.1)**. We assumed if a patient filled a prescription, they used it at least once; the term “use” was used to represent prescription fill.

Trend analysis: To look at differences in prescription fill patterns for secondary CHD prophylaxis over time we report the proportion of each P2Y12 inhibitors used among all patients initiating a P2Y12 inhibitor quarterly between 2013 and 2018 to show trends in treatment uptake over time. Trends were also evaluated by revascularization technique, whether invasive (i.e., PCI or CABG) or non-invasive (i.e., fibrinolysis).

High-risk comparison groups: We also examined prescribing patterns in two high-risk groups, patients: (i) high bleeding risk and (ii) with a history of stroke. High bleeding risk was defined as per AHA guidelines[165] by identifying patients with one of the following characteristics: (i) high-risk comorbidities in the past six months (i.e., diabetes mellitus, anemia, chronic kidney disease (CKD), and low body weight (LBW)) (ii) history of prior major bleeding (i.e., intracranial (IC), gastrointestinal (GI) and any other major bleeding)), and (iii) the concomitant use of oral anticoagulants, prescription NSAIDs, or steroids. We defined concomitant use of drugs if any of these high-risk medications were filled (i) within 15 days before or (ii) within 30 days after the index dispensing day of a P2Y12 inhibitor. Patients were also required to have at least 30 days’ supply of these high-risk medications to ensure concomitant use.

High risk use in patients with stroke was defined as a history of stroke or transient ischemic attack (TIA) in the prior 6 months. All the events were identified using international classification of disease 9 & 10 clinical modifications codes (ICD 9 & 10-CM) published previously **(Appendix Table 3.1)**.

Descriptive Variables

We grouped variables into three different categories based on (1) predisposing demographic, (2) enabling, and (3) need characteristics using ABM **(Figure 2.1)**.[134] Detailed information of the rationale for selected control variables is given in **Supplementary Material** under the confounder variables **section 3.6.1.**

Statistical Analysis

Descriptive statistics were used for categorical variables with counts and percentages. To examine influence of patient characteristics on the decision to prescribe a particular P2Y12 inhibitor, we used χ^2 testing. We tested for heterogeneity in age categories using the Breslow Day test and retained age as a categorical variable as it failed the null hypothesis of homogeneity Prescription prevalence of each P2Y12 inhibitor was described using counts and percent estimates. Additionally, given the deferring age characteristics in CCAE and MDCR samples, we studied both CCAE and MDCR study samples separately to study the effect of age on effectiveness outcomes.

In the longitudinal cross-sectional analysis to determine the prescription trend, the proportion of patients in every quarter (3-month incidence) on P2Y12 inhibitors was used as the primary variable. We used the Cochrane-Armitage test to observe if there was a significant difference in the trend among three months' prescription prevalence of each P2Y12 inhibitor for the years 2013 to 2018.

In addition to testing individual descriptive characteristics, we performed multivariate logistic regression to examine the influence of all variables in the ABM on the decision to prescribe individual P2Y12 inhibitors. Finally, we checked for the multi-

collinearity issue in the regression models to see if the independent variables in the models were correlated using “Variance Inflation Factor (VIF)” and “Tolerance Test.” We used VIF score of 10 to indicate a threshold for collinearity. None of the variables in our models had any multi-collinearity issue. All comparisons were considered significant at an α of 0.05; analyses were conducted using SAS 9.4.

3.3. Results

1. Description of Prescription Pattern of Different P2Y12 Inhibitors

We identified 92,734 and 44,339 patients with CHD who were revascularized after a CHD event in CCAE and MDCR samples, respectively. The CCAE and MDCR samples included 50,931 (54.9%), 15,146 (16.3%), and 26,657 (28.7%) and 33,697 (76.0%), 3,664 (8.3%), and 7,895 (17.8%) clopidogrel, prasugrel, and ticagrelor patients, respectively. Descriptive characteristics of P2Y12 inhibitor users for both samples are in **Appendix Table 3.2** with more detailed comparisons of P2Y12 inhibitors users **Supplementary Results (section 3.6.4)**.

a) Trends in P2Y12 Inhibitors use from 2013 to 2018

For the CCAE sample (**Appendix Table 3.3**), the prevalence of clopidogrel prescription decreased from 65.5% to 44.0% from 2013-2018. Similarly, prasugrel prescription decreased from 20.9% to 10.5%. However, ticagrelor prescription increased from 13.7% to 45.6% during the same period. Similar patterns were observed with the MDCR sample. Although in MDCR sample, clopidogrel prevalence decreased from 2013 to 2018, prevalence was higher than the CCAE sample over study period (79.4% in 2013 to 66.2% in 2018).

b) P2Y12 Inhibitor use by Revascularization Technique

After PCI, clopidogrel use decreased from 62.2% to 40.0% (2013 to 2018) in CCAE data while prasugrel use decreased from 22.9% to 11.2% **(Appendix Table 3.4)**. However, an increasing pattern was observed in the ticagrelor use (14.9% to 48.8%). Interestingly, in 2018, ticagrelor use was higher than clopidogrel (40.0% vs 48.8%). Yet,

for other revascularization techniques (i.e., CABG and Fibrinolysis), clopidogrel use was higher in the MDCR sample clopidogrel dominated the market share **(Appendix Table 3.5)**.

c) P2Y12 Inhibitors Use among Patients with High Bleeding Risk and History of Stroke or Trans Ischemic Events (TIA)

In CCAE patients with high bleeding risk, clopidogrel use decreased from 70.6% to 50.6% while ticagrelor use increased from 12.0% to 40.1% over study timeframe **(Appendix Table 3.6)**. Ticagrelor use increased substantially with time irrespective of bleeding risk. Although a similar pattern was seen in the MDCR sample clopidogrel was most used (82.2% in 2013 to 71.9% in 2018)

In patients with stroke or TIA history, clopidogrel was used most in both samples **(Appendix Table 3.7)**. Prasugrel was used in this population, but use was low compared to clopidogrel and ticagrelor.

2. P2Y12 Inhibitors Trends from 2013 to 2018

. Ticagrelor use surpassed clopidogrel use **(Appendix Figure 3.1)**, between the first and second quarters of 2018 in the CCAE sample. Although ticagrelor use increased over time in the MDCR sample, it remained well below clopidogrel use **(Appendix Figure 3.2)**. The trends in use over time were significant for each P2YI2 inhibitor ($p<0.05$) in both data samples. (**Appendix Tables 3.8 & 3.9**).

3. Predictors of P2Y12 Inhibitors Utilization in Both Sample Populations

We further looked at the predictors of drug selection in both of the data samples (**Tables 3.1 & 3.2**) using ABM controlling for predisposing, enabling, and need variables using multivariate logistic regression. With these adjusted comparisons, we explored if statistical significance persisted for the variables in exploratory analysis in **Appendix Table 3.2**. We also observed which individual categories in the categorical variables were statistically different and responsible for the significant difference at p=0.05 in the unadjusted comparisons. All the predictors as per ABM are discussed in detail in the *supplementary results section 3.6.4.* The most important clinical and non-clinical characteristics in the ABM associated with drug selection are described below:

a) Index year of P2Y12 inhibitor prescription:

Use of clopidogrel significantly decreased compared to ticagrelor in the CCAE sample **(Table 3.1)** after controlling for variables listed in Figure 1**.** Clopidogrel was associated with statistically significant 37% to 85% lower odds of use compared to ticagrelor (OR 0.63 (0.57-0.70)) and (OR 0.15 (0.14-0.17)), respectively in years 2014 and 2018 compared to 2013. Similarly, ticagrelor had significantly higher use than prasugrel in sample comparisons. For the MDCR sample **(Table 3.2)**, we saw a significant drop in clopidogrel use compared to ticagrelor with time as the odds of clopidogrel use reduction compared to ticagrelor reduced from 22% to 78% for the year 2014 to 2018 compared to 2013. Similarly, we observed a significant increase in the odds of ticagrelor use over the odds of prasugrel use increasing from 2.2 times to 6.8 times over the years (2015-2018 vs 2013).

b) Type of Revascularization

Of our CCAE sample, 8.7% underwent CABG and 90.6% PCI. Patients undergoing CABG versus PCI were more likely to use clopidogrel than ticagrelor (OR 1.73 (1.38-2.15)) in CCAE sample **(Table 3.1)**. Similarly, the odds of prasugrel versus ticagrelor use were lower for CABG compared to PCI patients (OR 0.67 (0.50-0.89)). For the MDCR sample, 10.2% underwent CABG and 89% PCI. We observed that the odds of clopidogrel use were higher compared to ticagrelor and prasugrel **(Table 3.2)** for those undergoing CABG versus PCI.

c) Type of Stent

Stents were implanted in 50.9% of our CCAE sample. Of these 45.4% were DES and 5.5% BMS. Among those with stent implantation, the odds of clopidogrel use were 14% lower compared to ticagrelor when patients were revascularized using drug eluting stents (DES) over bare metal stents (BMS) (OR 0.86 (0.80-0.92)). Similarly, clopidogrel was associated with lower use compared to prasugrel in patients revascularized using DES versus BMS (OR 0.86 (0.78-0.94)). For the MDCR sample, similarly, there was greater likelihood of newer P2Y12 inhibitors use over clopidogrel if DES were used compared to BMS for revascularization.

d) Type of ACS Presentation

In CCAE sample 25.0% presented with STEMI and 38.3% with NSTEMI/UA. Among patients with STEMI compared to NSTEMI/UA, in the CCAE sample **(Table 3.1)**, the odds of prescribing clopidogrel were lower in comparison to ticagrelor and prasugrel prescribing (OR 0.72 (0.69-0.76)) and (OR 0.76 (0.72-0.81)), respectively. We observed

a similar pattern in the MDCR sample **(Table 3.2)** as well. Additionally, we observed that ticagrelor was associated with 24% increased odds of being used compared to prasugrel (OR 1.24 (1.05-1.45)).

e) Comorbidities in the Past 6 Months

A higher category of the Elixhauser Index (EI) was associated with increased odds of clopidogrel use over ticagrelor for both of the study samples **(Tables 3.1 & 3.2).** The detailed description of P2Y12 inhibitors as per the EI index is presented in **Appendix Tables 3.10 & 3.11.**

f) High Bleeding Risk

We continued to see a difference in the odds of prescription fill of different P2Y12 agents among the patients at an increased risk of bleeding defined as per AHA.[41] Importantly, for the CCAE sample **(Table 3.1)**, patients with a history of prior bleeding within the last 6 months, clopidogrel was associated with 19% and 28% higher odds of being prescribed compared to ticagrelor (OR 1.19 (1.05-1.34)) and prasugrel (OR 1.28 (1.10-1.49)). We also looked at the P2Y12 inhibitors use concomitantly with high-risk medications as a risk of bleeding risk. We observed that clopidogrel was associated with 52% and 77% higher odds compared to ticagrelor (OR 1.52 (1.385-1.661)) and prasugrel (OR 1.77 (1.57-2.00)). Additionally, we observed 23% higher odds of ticagrelor prescription over prasugrel (OR 1.23 (1.07-1.41)). A similar pattern was observed in the MDCR sample **(Table 3.2).**

3.4. Discussion

These findings provide a comprehensive analysis of US real-world data for P2Y12 inhibitor utilization from 2013-2018. Our data show that ticagrelor became the preferred drug for secondary CHD prophylaxis for younger commercially insured patients (aged under 65 years). Newer P2Y12 inhibitors were preferred among the patients with STEMI versus NSTEMI/UA and managed with DES versus BMS. Whereas, clopidogrel was the preferred P2Y12 inhibitor in high bleeding risk, higher comorbidity indices, history of stroke/TIA, but not in those undergoing PCI. Prescribing patterns for most high-risk populations generally followed AHA/ACC guidelines However, 7.6 % CCAE and 5.2% MDCR patients with a stroke or TIA history were prescribed prasugrel, even though there is a black box warning by the FDA against its use in such patients.

Trends in utilization of P2Y12 Inhibitors

In patients younger than 65 (CCAE sample), ticagrelor use increased substantially from 2013 to 2018 surpassing clopidogrel use in 2018. Increasing ticagrelor use has been reported in previous observational studies. For example, ticagrelor use increased from 2% to 14% from 2012 to 2014 in Blue Cross Blue Shield of Michigan Cardiovascular Consortium data.[154] In UnitedHealthcare claims data combined prasugrel or ticagrelor use increased from 0% to 36.9% from 2008 to 2016[155]. However, clopidogrel remained the most utilized drug in these studies. In the present analysis, in 2018 ticagrelor exceeded clopidogrel in market share. Greater adoption of ticagrelor over clopidogrel with time in clinical practice in younger patients may have been impacted by PLATO trial results[26] in which ticagrelor use resulted in a significant reduction of death and MI without increased risk of major bleeding among patients with a median age of 62

years. Importantly, our study is the first to report ticagrelor as the drug of choice among patients who are below 65 years of age.

For the MDCR sample, clopidogrel remained the drug of choice for the entire study period. This trend might be because older age is associated with increased bleeding risk[135] and ticagrelor, because of its fast onset of action, may pose an increased risk in the elderly. Also, the active metabolites of prasugrel have been shown to increase bleeding risk among elderly patients.[166] Furthermore, clopidogrel use in an RCT studying an elderly population was associated with fewer bleeding events compared to prasugrel and ticagrelor,[46] which might explain the greater use of clopidogrel in the MDCR sample. However, some studies have reported no age-safety interaction [167] with a meta-analysis reporting consistent efficacy and safety in elderly and younger populations.[168] These conflicting results suggest the importance of a well-controlled RCT comparing these drugs in a US elderly population.

We also witnessed a substantial decrease in prasugrel use over time in both of the study samples. The trend toward greater ticagrelor use may stem from a lack of well controlled head-to-head RCTs with ticagrelor versus prasugrel in the US population. In a previous observational study, ticagrelor was associated with a reduced rate of recurrent cardiovascular and bleeding outcomes.[133] However, a meta-analysis of RCTs comparing prasugrel and ticagrelor reported no difference in clinical outcomes[169], with a network meta-analysis of RCTs pointing out more frequent stent thrombosis but no difference in overall efficacy and safety outcomes with ticagrelor compared to prasugrel.[170] Recently, ISAR-REACT-5[128], a multicentered RCT (2019) conducted in Europe, has reported better efficacy of prasugrel compared to ticagrelor in terms of death, MI, and stroke with

no difference in safety outcomes. It will be interesting to see if these results impact future practice in the US given that none of the study centers were in the US An observational study which took place 2 years after ticagrelor approval using a commercially insured US population signaled greater adoption of ticagrelor over prasugrel, [171] however those results are preliminary given the limited clinical experience with ticagrelor during the study period. Our results suggest that the trend toward greater adoption of ticagrelor over prasugrel continued to at least 2018, the latest date we had data available to study.

Prescription of P2Y12 Inhibitors by Revascularization Procedure

We also studied the adoption of P2Y12 inhibitors by different revascularization procedures given that potential differences in clinical outcomes by level of invasive technique used.[157-160] Among patients undergoing PCI, ticagrelor was used preferentially over clopidogrel or prasugrel by 2018 (CCAE sample). This could be due to the evidence that ticagrelor was more effective and safer in terms of overall bleeding than clopidogrel among patients undergoing PCI in the PLATO trial.[26] Also, an economic analysis reported greater cost-effectiveness with ticagrelor compared to a clopidogrel-based regimen from the perspective of the US health care system.[172,173] This might explain greater adoption of ticagrelor compared to clopidogrel in the CCAE sample. However, for the MDCR sample, clopidogrel was the preferred drug after PCI maybe because of the higher bleeding risk with newer drugs among the elderly population. Interestingly, for patients undergoing CABG, clopidogrel was the drug of choice in both of study samples. Higher use of clopidogrel post CABG appears to be rational, as clopidogrel has proven its efficacy in RCTs studying CABG patients.[174,175] Additionally, clopidogrel is recommended by AHA for a one-year post CABG to prevent graft occlusion.[176]

Nevertheless, there is no RCT evidence on the comparative effectiveness and safety of newer P2Y12 inhibitors post-CABG other than a post hoc analysis[177] of PLATO trial in which a similar efficacy of ticagrelor compared to clopidogrel was seen. There is a need for a comparative study to better understand the use of these drugs post CABG.

Prescription of P2Y12 Inhibitors by Clinical Characteristics

Among those at high bleeding risk, we observed that clopidogrel was the preferred drug for both of the study populations. These patterns are consistent with the findings in the PLATO and TIMI 38 trials which discovered increased risk of newer drugs for major bleeding.[26,118] Additionally, in a population-based study, ticagrelor was associated with a greater incidence of major bleeding.[65] Moreover, ticagrelor compared with clopidogrel resulted in greater bleeding events in an RCT studying an older population.[46] AHA guidelines also endorse the usage of clopidogrel among patients with increased risk of bleeding.[41] Thus, the associated bleeding risk with newer P2Y12 inhibitors might have resulted in greater use of clopidogrel among this high-risk population in our study samples.

We observed a greater adoption of ticagrelor in the CCAE sample compared to the MDCR sample, which may be due to the reason that the older population is at increased risk of major bleeding. Moreover, in the POPular Age RCT[46], clopidogrel was proven to have better efficacy and safety in the elderly population.

Clopidogrel had a higher use among those with a history of stroke or TIA. Interestingly, prasugrel was used in 5-8% of our study populations even though it has a black box warning against use in patients with a history of stroke/TIA[178]. A higher number of comorbid conditions in both populations were associated with greater

clopidogrel use in our study. A similar trend was observed in a multicenter prospective registry in which higher use of clopidogrel was reported compared to newer P2Y12 agents.[179]

Implications

Current AHA guidelines[41] for antiplatelet use recommend specific P2Y12 inhibitors depending on the patient clinical characteristics and the type of revascularization used to restore blood flow in the coronary arteries. We observed that the guidelines related to antiplatelet use in these two population samples were generally followed in our 2 study cohorts. However, we did see some differences which may be concerning given current guidelines and evidence. For example, the greater use of prasugrel among the patients with a history of stroke and TIA presents a risk of fatal bleeding[118] as reported in TRITON-TIMI 38 RCT. This prescribing pattern suggests a need for further study to determine whether or not there are safety concerns associated with this practice in real world populations. Additionally, this pattern suggest a need for further education of prescribers.

Ticagrelor utilization more than doubled in older population (MDCR) from 2013 to 2018. As the safety of ticagrelor is not well studied in the elderly population, there is a need to examine the potential implications of this prescribing trend in older patients. An open-label RCT in the Netherlands showed a greater risk of bleeding in the elderly population[46], thus a blinded RCT focused on an older US population may be warranted.

Strengths and Limitations

Our study has several strengths. First, the sample size for both of the populations under this study was large. We were able to differentiate the prevalence of P2Y12 inhibitor use across a younger and older population, but also examine patterns of use in patient subgroups undergoing different revascularization techniques and across a number of important patients' characteristic which influence the effectiveness and safety of these agents. Our analysis used the most current data with important information related to P2Y12 inhibitors use which may guide better management of CHD in the clinical practice.

Like any other observational study, this study also has several limitations. The trends observed in this study are only generalizable to the population studied. This population may differ from the typical patient with CHD in a number of ways. For example, the commercially insured population less than 65 is younger than the typical patient with CHD. Furthermore, the sample of patients in our Medicare sample had supplemental Medicare coverage and tend to be healthier and have more income than the typical Medicare patient. These factors could potentially bias the disease prevalence and prescription pattern of the P2Y12 inhibitors in our study. Additionally, MarketScan data lacks information related to race, ethnicity, socioeconomic status, frailty, and other factors that might have been of interest to examine trends in prescribing. These demographic factors are important as there are disparities in cardiovascular health reported in the previous studies. [180] [181] Finally, claims data do not capture over-the-counter prescription fills including low dose aspirin which is commonly prescribed and indicated in this population.[61]

3.5. Conclusion

In this study, we described the use of P2Y12 in great detail. We found that ticagrelor use increased over time in both of the data samples. In younger patients, ticagrelor exceeded the market share of clopidogrel in 2018; however, clopidogrel remained the most prescribed P2Y12 inhibitor in older patients with CHD undergoing revascularization. ,.Clopidogrel also remained the most popular P2Y12 inhibitor in patients with higher bleeding risk and comorbidities. Generally, practitioners followed AHA evidence-based guidelines in prescribing P2Y12 inhibitors. However, we also noted prasugrel use in patients with stroke or TA history, despite a black-box warning against its use.

Table 3. 1 Predictors of P2Y12 Inhibitors Utilization in the CCAE Population (Age ≤65 Years) Sample: MarketScan 2013-2018

Variables	Clopidogrel vs Ticagrelor				Clopidogrel vs Prasugrel				Ticagrelor vs Prasugrel			
	OR	95% CI		p value	OR	95% CI		p value	OR	95% CI		p value
PREDISPOSING DEMOGRAPHIC VARIABLES												
Age												
56-65 vs 18-45	1.11	1.02	1.20	**0.01**	1.16	1.05	1.27	<**0.01**	1.06	0.96	1.17	0.27
46-55 vs 18-45	1.03	0.95	1.12	0.51	1.04	0.94	1.15	0.45	1.03	0.93	1.15	0.54
Sex				<**0.01**								
Male vs Female	0.91	0.86	0.97	<**0.01**	0.79	0.73	0.85	<**0.01**	0.86	0.79	0.94	<**0.01**
Region												
Northeast vs South	1.04	0.97	1.12	0.24	1.46	1.33	1.59	<**0.01**	1.48	1.35	1.62	<**0.01**
North central vs South	1.11	1.04	1.18	<**0.01**	1.59	1.47	1.73	<**0.01**	1.50	1.38	1.63	<**0.01**
West vs South	1.56	1.44	1.69	<**0.01**	1.44	1.31	1.58	<**0.01**	0.94	0.85	1.04	0.21
Others vs South	1.31	1.04	1.65	0.02	1.13	0.90	1.40	0.29	0.88	0.67	1.15	0.34
ENABLING VARIABLES												
Plan type												
Comprehensive vs PPO	1.90	1.66	2.18	<**0.01**	0.83	0.72	0.95	<**0.01**	0.44	0.37	0.52	<**0.01**
EPO vs PPO	1.04	0.83	1.32	0.72	1.02	0.78	1.34	0.89	0.92	0.68	1.24	0.57
HMO vs PPO	1.08	1.00	1.18	0.06	1.09	0.99	1.21	0.09	1.04	0.93	1.16	0.51
POS vs PPO	1.02	0.93	1.13	0.63	1.16	1.03	1.31	0.02	1.16	1.02	1.32	0.02
POS with capitation vs PPO	0.94	0.73	1.20	0.59	1.32	0.95	1.84	0.09	1.62	1.15	2.30	0.01
CDHP vs PPO	0.91	0.84	0.98	0.02	0.98	0.88	1.08	0.63	1.08	0.97	1.20	0.17
HDHP vs PPO	1.05	0.95	1.15	0.35	1.01	0.89	1.14	0.91	0.99	0.87	1.12	0.82
Year of an index period												
2014 vs 2013	0.63	0.57	0.70	<**0.01**	0.99	0.90	1.10	0.90	1.60	1.42	1.81	<**0.01**
2015 vs 2013	0.43	0.38	0.47	<**0.01**	1.14	1.03	1.27	**0.01**	2.69	2.36	3.05	<**0.01**
2016 vs 2013	0.29	0.26	0.33	<**0.01**	0.95	0.85	1.05	0.30	3.26	2.87	3.71	<**0.01**
2017 vs 2013	0.19	0.17	0.21	<**0.01**	1.07	0.95	1.20	0.25	5.81	5.08	6.64	<**0.01**

2018 vs 2013	0.15	0.14	0.17	<**0.01**	1.17	1.03	1.32	**0.01**	7.77	6.78	8.91	<**0.01**
NEED VARIABLES												
Revascularization technique												
CABG vs PCI	1.73	1.38	2.15	<**0.01**	1.16	0.91	1.48	0.22	0.67	0.50	0.89	**0.01**
Fibrinolysis vs PCI	0.88	0.54	1.45	0.62	1.01	0.54	1.89	0.98	1.05	0.55	2.02	0.88
Stent type												
DES vs BMS	0.86	0.80	0.92	<**0.01**	0.86	0.78	0.94	<**0.01**	1.06	0.97	1.17	0.21
ACS type												
STEMI vs NSTEMI	0.72	0.69	0.76	<**0.01**	0.76	0.72	0.81	<**0.01**	1.05	0.98	1.12	0.14
Elixhauser index (Readmission)												
Cat 1 vs Cat 0	1.10	1.03	1.17	<**0.01**	0.96	0.89	1.04	0.3	0.89	0.82	0.96	<**0.01**
Cat 2 vs Cat 0	1.15	1.04	1.28	<**0.01**	1.10	0.96	1.24	0.16	0.98	0.85	1.12	0.75
Cat 3 vs Cat 0	1.15	1.07	1.25	<**0.01**	1.10	1.01	1.21	0.03	0.98	0.89	1.08	0.65
Cat 4 vs Cat 0	1.17	1.06	1.28	<**0.01**	1.21	1.07	1.36	<**0.01**	1.10	0.97	1.25	0.15
High bleeding risk												
Diabetes (Past 6 months) ELX	1.02	0.95	1.10	0.6	0.94	0.86	1.03	0.17	0.90	0.81	0.99	**0.03**
CKD (Past 6 months)	1.20	1.04	1.37	<**0.01**	1.23	1.04	1.46	**0.01**	1.01	0.84	1.22	0.91
LBW (Past 6 months)	1.68	1.10	2.55	**0.02**	1.87	1.03	3.39	**0.04**	1.05	0.53	2.07	0.88
Anemia (Past 6 months)	1.00	0.85	1.17	0.99	1.05	0.86	1.29	0.62	1.10	0.87	1.38	0.43
History of Prior Bleeding (Six months): Intracranial, GI bleeding, and other major bleeding	1.19	1.05	1.34	<**0.01**	1.28	1.10	1.49	<**0.01**	1.03	0.87	1.22	0.71
Concomitant use of high risk meds (Oral anticoagulants, NSAIDS, and corticosteroids)	1.52	1.39	1.66	<**0.01**	1.77	1.57	2.00	<**0.01**	1.23	1.07	1.41	<**0.01**
Prescription Medications in the past 6 months												
Antiplatelet drugs	0.89	0.79	1.00	0.06	0.81	0.71	0.93	<**0.01**	0.94	0.81	1.09	0.4
Antihypertensive medications												
Ace Inhibitors	1.11	1.04	1.19	<**0.01**	1.01	0.93	1.09	0.9	0.92	0.84	1.00	0.06
Alpha beta inhibitors	1.22	0.82	1.80	0.32	1.17	0.71	1.95	0.53	1.11	0.64	1.94	0.71
Beta blockers	1.23	1.15	1.31	<**0.01**	1.11	1.03	1.21	**0.01**	0.90	0.83	0.99	**0.02**
Calcium channel blockers	0.99	0.92	1.07	0.82	1.06	0.97	1.16	0.19	1.08	0.98	1.19	0.13
Angiotensin II blockers	0.97	0.90	1.05	0.44	0.98	0.89	1.07	0.58	1.00	0.91	1.10	0.99

Antiarrhythmic drugs	1.78	1.23	2.58	<**0.01**	1.29	0.84	1.98	0.24	0.78	0.46	1.33	0.36
Cardiac Glycosides	2.26	1.31	3.91	<**0.01**	1.63	0.91	2.90	0.09	0.70	0.33	1.49	0.35
Antidiabetics												
Miscellaneous antidiabetics *(Biguanides, GLP-1 analogues DPP4, alpha-glucoside inhibitors, incretin mimetics, amylin analogues, glucagon, and combinations)*	0.92	0.84	1.01	0.09	0.92	0.83	1.03	0.16	1.00	0.88	1.12	0.94
Sulfonylureas	1.07	0.95	1.20	0.25	1.12	0.97	1.28	0.12	1.02	0.87	1.19	0.83
Meglitinides	0.59	0.31	1.12	0.11	0.62	0.29	1.31	0.21	0.97	0.44	2.12	0.93
SGLT	0.80	0.66	0.96	**0.01**	0.88	0.69	1.11	0.28	1.22	0.96	1.54	0.1
TZD	1.00	0.77	1.30	0.99	0.87	0.64	1.18	0.36	0.92	0.66	1.29	0.63
Anti-lipid drugs	0.95	0.89	1.00	0.06	0.88	0.82	0.95	<**0.01**	0.95	0.88	1.02	0.15
Diuretics												
Loop diuretics	1.15	1.00	1.32	0.06	1.27	1.06	1.51	<**0.01**	1.15	0.94	1.40	0.18
Thiazide diuretics	1.04	0.94	1.16	0.44	1.04	0.91	1.18	0.57	1.02	0.88	1.17	0.82
Potassium spring agents	1.20	1.01	1.41	**0.03**	1.06	0.87	1.30	0.57	1.01	0.81	1.27	0.93
Carbonic anhydrase inhibitors	1.32	0.59	2.94	0.5	1.07	0.42	2.74	0.89	0.90	0.31	2.65	0.84
Antacids												
PPIs	0.95	0.88	1.02	0.13	0.89	0.82	0.97	<**0.01**	0.97	0.89	1.06	0.49
H2RA	0.97	0.82	1.16	0.76	1.12	0.89	1.40	0.34	1.08	0.85	1.39	0.51
Anti-depressants	0.96	0.90	1.03	0.27	1.00	0.92	1.09	0.98	1.03	0.94	1.13	0.55
Estrogen	0.89	0.72	1.10	0.27	0.81	0.63	1.05	0.11	0.95	0.72	1.25	0.68

Acronyms: CCAE: MarketScan Commercial Claims and Encounters database, EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; DES: drug-eluting stent; BMS: bare-metal stent; ACS: acute coronary syndrome; STEMI: ST wave elevated myocardial infarction; NSTEMI: Non-ST elevated myocardial infarction; UA: unstable angina; CCI: Charlson's comorbidity index; AHA: American Heart Association; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: Sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Table 3. 2 Predictors of P2Y12 Inhibitors Utilization in the MDCR (Age ≥65 Years) Population Sample: MarketScan 2013-2018

Variables	Clopidogrel vs Ticagrelor				Clopidogrel vs Prasugrel				Ticagrelor vs Prasugrel			
	OR	95% CI		p value	OR	95% CI		p value	OR	95% CI		p value
PREDISPOSING DEMOGRAPHIC VARIABLES												
Age												
Above 85 years vs 65-74	2.36	2.01	2.77	**<0.01**	8.94	6.03	13.25	**<0.01**	3.88	2.53	5.94	**<0.01**
75-84 vs 65-74	1.41	1.28	1.56	**<0.01**	3.20	2.72	3.77	**<0.01**	2.33	1.93	2.80	**<0.01**
Sex												**<0.01**
Male vs Female	1.01	0.92	1.11	0.83	0.77	0.66	0.90	**<0.01**	0.78	0.66	0.93	**<0.01**
Region												
Northeast vs South	1.10	0.96	1.26	0.15	1.45	1.18	1.77	**<0.01**	1.28	1.02	1.60	**0.03**
Northcentral vs South	1.22	1.09	1.36	**<0.01**	1.55	1.31	1.84	**<0.01**	1.38	1.14	1.67	**<0.01**
West vs South	1.36	1.15	1.59	**<0.01**	1.31	1.05	1.65	**0.02**	0.95	0.73	1.24	0.70
Others vs South	0.63	0.33	1.18	0.15	0.66	0.35	1.25	0.19	0.92	0.43	1.97	0.83
ENABLING VARIABLES												
Plan type												
Comprehensive vs PPO	0.95	0.86	1.05	0.33	0.95	0.81	1.11	0.48	0.97	0.81	1.16	0.72
EPO vs PPO	0.65	0.34	1.25	0.19	0.84	0.33	2.12	0.70	1.13	0.41	3.09	0.82
HMO vs PPO	1.30	1.12	1.53	**<0.01**	1.15	0.92	1.43	0.22	0.85	0.66	1.09	0.20
POS vs PPO	1.15	0.89	1.49	0.27	1.10	0.75	1.60	0.63	0.98	0.64	1.51	0.93
POS with capitation vs PPO	0.86	0.60	1.24	0.42	1.04	0.54	1.98	0.91	1.22	0.62	2.42	0.57
CDHP vs PPO	0.56	0.36	0.88	**0.01**	1.09	0.52	2.29	0.82	1.50	0.69	3.26	0.31
HDHP vs PPO	1.12	0.59	2.13	0.72	1.97	0.68	5.67	0.20	2.28	0.71	7.35	0.17
Year of the index period												
2014 vs 2013	0.78	0.66	0.93	**<0.01**	0.86	0.71	1.06	0.15	1.11	0.86	1.42	0.42
2015 vs 2013	0.48	0.40	0.56	**<0.01**	1.08	0.87	1.35	0.47	s	1.75	2.96	**<0.01**
2016 vs 2013	0.40	0.33	0.48	**<0.01**	0.95	0.75	1.21	0.67	2.40	1.82	3.17	**<0.01**
2017 vs 2013	0.31	0.26	0.38	**<0.01**	1.22	0.93	1.61	0.15	4.07	2.99	5.55	**<0.01**
2018 vs 2013	0.22	0.18	0.27	**<0.01**	1.45	1.02	2.07	**0.04**	6.88	4.72	10.03	**<0.01**
NEED VARIABLES												

Revascularization technique												
CABG vs PCI	1.30	1.03	1.65	**0.03**	1.53	1.04	2.24	**0.03**	1.13	0.73	1.76	0.58
Fibrinolysis vs PCI	0.83	0.25	2.79	0.76	0.45	0.09	2.23	0.32	0.77	0.12	4.80	0.78
Stent type												
DES vs BMS	0.81	0.71	0.92	**<0.01**	0.67	0.54	0.83	**<0.01**	0.86	0.68	1.10	0.23
ACS type												
STEMI vs NSTEMI	0.65	0.59	0.71	**<0.01**	0.74	0.64	0.85	**<0.01**	1.24	1.05	1.45	**0.01**
Elixhauser index (Readmission)												
Cat 1 vs Cat 0	1.11	0.97	1.26	0.12	1.04	0.86	1.27	0.67	0.93	0.74	1.15	0.48
Cat 2 vs Cat 0	1.09	0.90	1.32	0.39	1.56	1.12	2.16	**<0.01**	1.37	0.95	1.96	**0.09**
Cat 3 vs Cat 0	1.24	1.08	1.42	**<0.01**	0.94	0.78	1.15	0.55	0.78	0.62	0.98	**0.03**
Cat 4 vs Cat 0	1.21	1.05	1.39	**<0.01**	1.23	0.98	1.53	0.07	1.02	0.79	1.32	0.86
High bleeding risk												
Diabetes (Past 6 months)	1.08	0.95	1.22	0.26	0.95	0.79	1.155	0.63	0.92	0.73	1.15	0.46
CKD (Past 6 months)	1.11	0.96	1.29	0.17	1.05	0.83	1.33	0.70	0.94	0.71	1.24	0.65
LBW (past 6 months)	1.92	1.12	3.26	**0.02**	2.6	0.94	7.21	0.06	1.55	0.48	4.97	0.46
Anemia (Past 6 months)	0.79	0.65	0.97	**0.02**	1.11	0.80	1.54	0.54	1.33	0.91	1.95	0.13
History of Prior bleeding (Six months): Intracranial, GI bleeding, and other major bleeding	1.41	1.18	1.67	**<0.01**	1.07	0.83	1.38	0.61	0.74	0.55	1	**0.049**
Concomitant use of high risk meds (Oral anticoagulants, NSAIDS, and corticosteroids)	1.8	1.56	2.08	**<0.01**	1.59	1.28	1.975	**<0.01**	0.85	0.66	1.10	0.22
Prescription medications in the past 6 months												
Antiplatelet drugs	0.78	0.68	0.91	**<0.01**	0.87	0.69	1.08	0.20	1.05	0.81	1.36	0.71
Antihypertensive medications												
Ace inhibitors	1.01	0.90	1.13	0.89	1.02	0.86	1.21	0.82	0.97	0.80	1.17	0.74
Alpha-beta inhibitors	2.60	1.32	5.12	**<0.01**	2.74	0.85	8.86	0.09	1.06	0.27	4.20	0.93
Beta blockers	1.17	1.05	1.29	**<0.01**	1.10	0.94	1.28	0.23	0.95	0.80	1.14	0.60
Calcium channel blockers	1.09	0.98	1.21	0.12	1.08	0.92	1.28	0.33	0.97	0.81	1.17	0.76

Angiotensin II blockers	0.91	0.81	1.02	0.09	0.98	0.82	1.17	0.79	1.15	0.94	1.40	0.17
Antiarrhythmic drugs	1.14	0.82	1.60	0.42	0.99	0.60	1.61	0.95	0.91	0.51	1.64	0.75
Cardiac glycosides	1.26	0.86	1.85	0.23	1.87	0.94	3.72	0.08	1.63	0.74	3.58	0.23
Antidiabetics												
Miscellaneous antidiabetics *(Biguanides, GLP-1 analogues DPP4, alpha-glucoside inhibitors, incretin mimetics, amylin analogues, glucagon, and combinations)*	0.87	0.75	1.01	0.07	0.97	0.78	1.21	0.78	0.98	0.76	1.26	0.86
Sulfonylureas	0.97	0.82	1.15	0.70	1.24	0.95	1.61	0.12	1.34	0.99	1.82	0.06
Meglitinides	1.18	0.64	2.18	0.59	1.32	0.46	3.79	0.60	1.39	0.42	4.61	0.59
SGLT	0.77	0.49	1.23	0.27	1.01	0.46	2.20	0.99	1.50	0.65	3.47	0.34
TZD	1.41	0.87	2.27	0.16	0.71	0.41	1.23	0.22	0.52	0.26	1.05	0.07
Anti-lipid drugs	1.03	0.93	1.13	0.60	0.93	0.80	1.08	0.30	0.92	0.78	1.09	0.34
Diuretics												
Loop diuretics	1.21	1.04	1.40	**0.01**	1.17	0.92	1.48	0.20	0.96	0.73	1.26	0.76
Thiazide diuretics	1.03	0.88	1.21	0.68	0.94	0.75	1.18	0.59	0.86	0.66	1.13	0.28
Potassium spring agents	1.06	0.86	1.32	0.56	0.97	0.70	1.34	0.84	0.87	0.60	1.27	0.47
Carbonic anhydrase inhibitors	0.44	0.18	1.08	0.07	>999.999	<0.001	>999.999	0.96	>999.999	<0.001	>999.999	0.97
Antacids												
PPIs	1.08	0.97	1.20	0.18	1.07	0.91	1.26	0.44	0.97	0.80	1.17	0.75
H2RA	0.94	0.75	1.17	0.56	1.07	0.75	1.53	0.69	1.02	0.69	1.52	0.92
Anti-depressants	1.19	1.05	1.35	**0.01**	0.98	0.82	1.17	0.82	0.86	0.70	1.07	0.17
Estrogen	0.99	0.72	1.35	0.94	1.05	0.65	1.72	0.84	0.86	0.49	1.50	0.59

Acronyms: MDCR: Medicare Supplemental and coordination of benefits (COB) Database, EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; DES: drug-eluting stent; BMS: bare-metal stent; ACS: acute coronary syndrome; STEMI: ST wave elevated myocardial infarction; NSTEMI: Non-ST elevated myocardial infarction; UA: unstable angina; CCI: Charlson's comorbidity index; AHA: American Heart Association; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: Sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

3.6. Supplementary Materials

This section contains the supporting material for the text in the main manuscript in the following order: control variables, identification codes for disease and procedure, supplementary tables, and supplementary results.

3.6.1. Confounder Variables

We grouped variables into three different categories based on (1) predisposing demographic, (2) enabling, and (3) need characteristics using Andersen's Behavioral Model for Health Services Utilization.[134] As per this model, healthcare utilization and health outcomes are affected by these characteristics of the population. For example,

(1) Predisposing variables in this study included age, gender, and the geographical region of the service which might predispose the patients to the utilization of healthcare services. We considered patients' age as a potential predisposing factor because older age is associated with increased bleeding risk[135]. As newer P2Y12 inhibitors are associated with a high risk of major bleeding compared to clopidogrel, clinicians might choose safer antiplatelet drugs in the older population which may result in a differential pattern of prescribing. Literature suggests a significant state-level variation in cardiovascular health in the US.[136] These differences in cardiovascular health may affect the prescription of P2Y12 inhibitors which will be explored in this study. Furthermore, female sex has been shown to have increased bleeding risk which could incline clinicians towards safer antiplatelet drug prescription, thus, we used gender as a predisposing demographic variable in this study.

(2) Enabling characteristics potentially render or impede the use of healthcare services. This set of variables in our study comprised of the type of insurance plan/coverage, and the year of the index date. We considered a type of insurance plan as an enabling variable because variation in the prescription drug coverage has been observed which may influence the patient's and physician's choices of treatment depending on whether a specific plan covers the choice of drug.[137] With time the adoption of newer P2Y12 inhibitors is seen in the clinical practice post-FDA approval of these drugs. As the availability of newer medications with time may enable the physicians to choose from the available P2Y12 inhibitors as per the patient's characteristics, we used the index year of antiplatelet drug use as an enabling variable.

(3) Finally, we included several need variables in our model which may represent both the perceived and actual health condition of a patient that mandates the utilization of healthcare services. We included mode of revascularization, type of stents, type of ACS presentation, prior comorbidities in the form of Elixhauser comorbidity index (EI) for readmission, high bleeding risk, and medication history in the past six months.

We included the mode of revascularization as our need variable because the technique may vary depending on the patients' need for a particular revascularization method. For example, high-risk patients with multiple diagnoses of infarct in a single coronary artery may require CABG compared to PCI; whereas, PCI may be sufficient to revascularize a culprit artery. However, in the scarcity of the facility to perform a CABG or PCI, patients may be in immediate need of a fibrinolytic therapy on presentation in an ER. Given that the recommended treatment with P2Y12 inhibitors varies, which may

impact the decision for prescription, we opted for the mode of revascularization as a need variable.

We considered the type of stent as another need variable because current guidelines for antiplatelet therapy vary depending on whether bare-metal stent (BMS) or drug-eluting stent (DES) is used in PCI. For BMS current guidelines recommends treatment with antiplatelet medications for at least one month; whereas, for DES, the recommendations are to prescribe medications for 6-12 months.[138] The need for long-term treatment with newer P2Y12 inhibitors can be expensive because of the unavailability of generic versions, which may cause a substantial burden of out-of-pocket payment on the patients. Thus, the cost of treatment depending on the type of stent may affect the clinicians' decision for the P2Y12 prescription.

Furthermore, we included the type of ACS presentation whether STEMI or NSTEMI/UA as a need variable because STEMI is an emergency situation, needs immediate treatment, and the course of treatment can be different compared to NSTEMI/UA. STEMI patients are younger compared to NSTEMI[139] which may incline clinicians towards the use of newer P2Y12 inhibitors. Additionally, newer P2Y12 inhibitors are potent and have superior efficacy in STEMI patients compared to clopidogrel,[140] which may cause a discrepancy in the prescription of P2Y12 inhibitors further. We differentiated STEMI and NSTEMI patients using validated and published ICD 9 and 10 codes with high sensitivity.[141-143]

Previous comorbid conditions may cause a variation in the decision to prescribe the type of P2Y12 inhibitors among patients with coronary heart disease. Studies have reported increased use of newer P2Y12 inhibitors and better clinical outcomes in terms

of major cardiac events among the patients with fewer comorbidities; whereas increased use of clopidogrel has been reported among patients with more associated comorbidities.[144,145] These factors may reflect in the discrepancies in the prescription of these agents as well. To guide the comorbidities as a need variable in our model, we utilized the EI index. We categorized the EI index into five different categories based on EI scores: (i) EI < 0 as category 0, (ii) EI=0 as category 1, (iii) EI=1 to 5 as category 2, (iv) EI= 6-13 as category 3, and (iv) EI >=14 as category 4 as previously published and tested in coronary heart disease.[146] All ICD codes to identify Elixhauser conditions were taken from *Elixhauser Comorbidity Software, Version 3.7*.[114]

Bleeding risk with P2Y12 inhibitors is a serious concern, and newer P2Y12 inhibitors are associated with increased bleeding risk in the RCTs and a meta-analysis.[148] This association may cause clinicians to choose clopidogrel over newer P2Y12 inhibitors among those who are at increased risk of major bleeding. We used AHA guidelines [41]to identify high bleeding risk population. We used any history of high-risk comorbid conditions (i.e., diabetes, anemia, chronic kidney disease, low body weight), any major bleeding (i.e., intracranial, gastrointestinal, and any other major bleeding) in the last 6 months to determine if patients were at increased risk of major bleeding. We also included any concomitant use of the medication linked to higher bleeding risk i.e., oral anticoagulants, prescription non-steroidal anti-inflammatory drugs (NSAIDs), or corticosteroids as an additional bleeding risk as per AHA recommendations.

Finally, we also considered the history of medications in the past 6 months. We considered the use of anticoagulants, antiplatelet drugs, antiarrhythmic drugs,

antihypertensives, antidiabetics, diuretics, antacids based on the studies published previously.[64,133,149,150] We included antidepressant therapy as a need variable because of the association of antidepressants with increased risk of MI.[151,152] This increased risk of MI may require a higher need for aggressive antiplatelet therapy which may cause a physician to prescribe newer antiplatelet drugs compared to clopidogrel. Additionally, we further included estrogen as its use is associated with increased risk of thrombosis[153] which might need aggressive antiplatelet therapy as well.

We used the previously published ICD and CPT codes to identify the control variables described in the following section.

3.6.2. Codes for Disease and Procedure Identification

Appendix Table 3. 1 International Classification of Disease 9 & 10 Clinical Modifications, Current Diagnosis Procedure Codes, and Healthcare Common Procedure Coding System Codes

Revascularizations	**Percutaneous Coronary Intervention (PCI):** **ICD 9 Procedure codes:** '0066' '3601' '3602' '3603' '3605' '3606' '3607' '3609' **ICD 10 Procedure codes:** '0270346' '027034Z' '0270356' '027035Z' '0270366' '027036Z' '0270376' '027037Z' '02703D6' '02703DZ' '02703ZZ' '0270046' '0271346' '027134Z' '0271356' '027135Z' '0271366' '027136Z' '0271376' '027137Z' '02713D6' '02713DZ' '02714E6' '02713EZ' '02714EZ' '02723FZ' '02733GZ' '02713E6' '02723F6' '02733G6' '0272366' '0273376' '027236Z' '027337Z' '02C03ZZ' '02C13ZZ' '02C23ZZ' '02C33ZZ' '02C03Z6' '02C13Z6' '02C23Z6' '02C33Z6' '92980' '92981' '92982' '92984' '92920' '92924' '92925' '92921' '92928' '92929' '92933' '92934' '37184' '37185' '37186' '37187' '37188' 'C9600' 'C9601' 'C9602' 'C9603' 'G0290' 'G0291' **Coronary Artery Bypass Graft (CABG):** **ICD 9 Procedure codes:** '361' '3610' '3611' '3612' '3613' '3614' '3615' '3616' '3617' '3619' '362' '0210' **ICD 10 Procedure codes:** '021009W' '02100A3' '02100A8' '02100A9' '02100AC' '02100AF' '02100AW' '33510' '33511' '33512' '33513' '33514' '33516' '33517' '33518' '33519' '33520' '33521'

	'33522' '33523' '33530' '33533' '33534' '33535' '33536' '33545' '92937' '92938' 'C9604' 'C9605' 'C9606' **Fibrinolysis:** **ICD 9 Procedure codes:** '9910' '3604' **ICD 10 Procedure codes:** '3E07' '3E07017' '3E07317' '3E07017' '3E07317' '3E08017' '3E08317' 'J2993' 'J2995' 'J2997' 'J0350' 'J3101' '32561' '32562' '86590' '36593'
Coronary Heart Disease	**ICD 9 CM codes:** 410.XX: Acute myocardial infarction 411.XX: Other acute and subacute forms of ischemic heart disease 412.XX: Old MI 413.XX: Angina pectoris 414.XX: Other forms of chronic ischemic heart disease 429.XX: Ill-defined descriptions and complications of heart disease **ICD 10 CM Codes:** I20.XX: **Angina Pectoris** I21.XX: Acute myocardial infarction I22.XX: Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction I23.XX: Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction I24.XX: Other acute ischemic heart diseases I25.XX: Chronic ischemic heart disease R94.30 and R94.31: Abnormal EKG
High Bleeding Risk	**1. Diabetes** "E1100", "E1101", "E1110", "E1111", "E119", "25000", "25002", "25010", "25012", "25020", "25022", "25030", "25032", "E1121", "E1122", "E1129", "E11311", "E11319", "E11321", "E113211", "E113212", "E113213", "E113219", "E11329", "E113291", "E113292", "E113293", "E113299", "E11331", "E113311", "E113312", "E113313", "E113319", "E11339", "E113391", "E113392", "E113393", "E113399", "E11341", "E113411", "E113412", "E113413", "E113419", "E11349","E113491", "E113492", "E113493", "E113499", "E11351", "E113511", "E113512", "E113513", "E113519", "E113521", "E113522", "E113523", "E113529", "E113531", "E113532", "E113533", "E113539", "E113541", "E113542", "E113543", "E113549", "E113551", "E113552", "E113553", "E113559", "E11359", "E113591", "E113592", "E113593", "E113599", "E1136", "E1137X1", "E1137X2", "E1137X3", "E1137X9", "E1139", "E1140", "E1141", "E1142", "E1143", "E1144", "E1149", "E1151", "E1152", "E1159", "E11610", "E11618", "E11620", "E11621", "E11622", "E11628", "E11630", "E11638","E11641", "E11649", "E1165", "E1169", "E118", "25040", "25042", "25050", "25052", "25060", "25062", "25070", "25072", "25080", "25082", "25090","25092" **2. Anemia** "D501", "D508", "D509", "D510", "D511", "D512", "D513", "D518", "D519", "D520", "D521", "D528", "D529", "D530", "D531", "D532", "D538", "D539", "D630","D631", "D638", "D649", "2801", "2808", "2809", "2810", "2811", "2812", "2813", "2814", "2818", "2819", "28521", "28522", "28529", "2859"

	3. Low body weight "E40", "E41", "E42", "E43", "E440", "E441", "E45", "E46", "E640", "R634", "R636", "260", "261", "262", "2630", "2631", "2632", "2638", "2639", "78321", "78322" **4. Chronic Kidney Disease** ("N181", "N182", "N183","N184","N185","N186","N189","N19", "Z4901","Z4902","Z4931","Z4932","Z9115","Z940","Z992", "5851", "5852","5853", "5854", "5855", "5856", "5859", "586","V420", "V451", "V560", "V561", "V562", "V5631", "V5632", "V568", "V4511", "V4512" **5. History of Bleeding** **a. Gastrointestinal Bleeding** '53100' '53101' '53120' '53121' '53140' '53141' '53160' '53161' '53200' '53201' '53220' '53221' '53240' '53241' '53260' '53261' '53300' '53301' '53320' '53321' '53340' '53341' '53360' '53361' '53400' '53401' '53420' '53421' '53440' '53441' '53460' '53461' '53501' '53511' '53521' '53531' '53541' '53551' '53561' '53783' '56202' '56203' '56212' '56213' '56985' '45620' '5307' '53082' '53500' '53510' '53520' '53530' '53540' '53550' '53560' '56200' '56201' '56210' '56211' '56881' '4560' '5311' '5313' '5315' '5317' '5319' '5321' '5323' '5325' '5327' '5329' '5331' '5333' '5335' '5337' '5339' '5341' '5343' '5345' '5347' '5349' '5301' '4552' '4555' '4558' '5693' '5781' '5789' '5780' '4550' '4551' '4553' '4554' '4556' '4557' '4559' 'K20' 'K250' 'K252' 'K254' 'K256' 'K260' 'K262' 'K264' 'K266' 'K270' 'K272' 'K274' 'K276' 'K280' 'K282' 'K284' 'K286' 'K226"K228' 'K920' 'K661' 'K625' 'K921' 'K922' 'K251' 'K253' 'K255' 'K257' 'K259' 'K261' 'K263' 'K265' 'K267' 'K269' 'K271' 'K273' 'K275' 'K277' 'K279' 'K281' 'K283' 'K285' 'K287' 'K289' 'K661' 'K2901' 'K2941' 'K2951' 'K2961' 'K2921' 'K2971' 'K2991' 'K2981' 'I8501' 'I8511' 'K5701' 'K5711' 'K5713' 'K5721' 'K5731"K5733' 'K5741' 'K5751' 'K5753' 'K5781' 'K5791' 'K5793' 'K5521' 'K2900' 'K2940' 'K2950' 'K2960' 'K2920' 'K2970' 'K2990' 'K2980' 'K5700' 'K5710' 'K5712' 'K5720' 'K5730' 'K5732' 'K5740' 'K5750' 'K5752' 'K5780' 'K5790' 'K5792' 'K31811' **b. Intracranial Bleeding** '430' '431' '4320' '4321' '4329' 'I60' 'I61' 'I62' '852', '8530' **c. Any other Bleeding:** '0786', '2463', '2851', '2865', '38869', '36043', '36243', '36281', '36361', '36362', '36372', '36441', '37272', '37481', '37632', '37742', '37923', '4230', '4590', '59381', '5967', '5997', '6021', '6201', '6214', '6262', '6265', '6267', '6268', '6269', '640', '6419', '6661', '7191', '7827', '7847', '7848', '7863', '79001', '9582', '99702', '99811' '71910' '71911' '71912' '71913' '71914' '71915' '71916' '71917' '71918' '71919' '79092' '5997' '6238' '6262' '6266' '4230' '4590' '7847' '7848' '7863' '2800' '2859' 'R31' 'R58' 'D62' 'N920' 'N921' 'I312' 'K661' 'M250' 'R040' 'R041' 'R042' 'D500' 'D649' 'R791'
Stroke/Trans ischemic events	'430' , '431' , '432' , '433' , '434' , '435' , '436' , 'I60' , 'I61' , 'I62' , 'I63' , 'I64'

3.6.3. Supplementary Tables

Appendix Table 3. 2 Demographics and Baseline Characteristics in the CCAE (Age ≤65 Years) and MDCR (Age ≥65 Years): MarketScan 2013-2018 Populations

	CCAE Sample (N=92,734)				MDCR Sample (N=44,339)			
	Clopidogrel (n1=50931)	Prasugrel (n2=15146)	Ticagrelor (n3=26657)	P-Value	Clopidogrel (n1= 33697)	Prasugrel (n2= 3664)	Ticagrelor (n3=7895)	P-Value
PREDISPOSING DEMOGRAPHIC VARIABLES								
AGE CATEGORY				**<.001**				**<.001**
>=85 years(MDCR)	NA	NA			3982(12.04)	103(2.9)	575(7.44)	
75-84 years(MDCR)	NA	NA			13077(39.55)	744(20.98)	2758(35.7)	
65-74 years(MDCR)	NA	NA			16008(48.41)	2700(76.12)	4392(56.85)	
56-65 Years(CCAE)	30394 (60.74%)	8312 (54.88%)	14646 (54.94%)	**<.001**	NA	NA	NA	
46-55 Years(CCAE)	15920 (31.26%)	5274 (34.82%)	9270(34.78%)		NA	NA	NA	
36-45 Years(CCAE)	3722 (7.31%)	1412 (9.32%)	2456 (9.21%)		NA	NA	NA	
26-35 Years(CCAE)	320 (0.63%)	136 (0.90%)	269 (1.01%)		NA	NA	NA	
18-25 Years(CCAE)	35 (0.07%)	12 (0.08%)	16 (0.06%)		NA	NA	NA	
SEX				**<.001**				
Male	38554 (75.70%)	12022 (79.37%)	20608 (77.31%)		21792(65.9)	2564(72.29)	5099(66.01)	**<.001**
REGION				**<.001**				
Northeast	8639 (16.94%)	2315 (15.28%)	4954 (18.58%)		7224(21.85)	805(22.7)	1853(23.99)	
Northcentral	12156(23.87)	2936 (19.38%)	6160 (23.11%)		11477(34.71)	991(27.94)	2516(32.57)	
South	22960 (45.08%)	7840 (51.76%)	12560 (47.12%)		10544(31.89)	1304(36.76)	2578(33.37)	
West	6568 (12.90%)	1826 (12.06%)	2792 (10.47%)		3699(11.19)	416(11.73)	741(9.59)	
Unknown	618 (1.21%)	229 (1.51%)	191 (0.72%)		123(0.37)	31(0.87)	37(0.48)	
ENABLING VARIABLES								
PLAN TYPE				**<.001**				**<.001**
Comprehensive	2343 (4.60%)	733 (4.84%)	689 (2.58%)		13003(39.32)	1267(35.72)	2993(38.74)	
EPO	516 (1.01%)	156 (1.03%)	253 (0.95%)		85(0.26)	14(0.39)	45(0.58)	

HMO	5239 (10.29%)	1345 (8.88%)	2487 (9.33%)		3514(10.63)	338(9.53)	707(9.15)	
POS	3720 (7.30%)	993 (6.56%)	1960 (7.35%)		1349(4.08)	160(4.51)	289(3.74)	
PPO	29263 (57.46%)	8952 (59.10%)	15236 (57.16%)		14117(42.69)	1644(46.35)	3356(43.44)	
POS with Capitation	384 (0.75%)	97 (0.64%)	241 (0.90%)		302(0.91)	24(0.68)	111(1.44)	
CDHP	5068 (9.95%)	1597 (10.54)	3259 (12.23%)		257(0.78)	55(1.55)	103(1.33)	
HDHP	3151 (6.19%)	922 (6.09%)	1935 (7.26%)		104(0.31)	16(0.45)	42(0.54)	
YEAR (INDEX DATE)				**<.001**				**<.001**
2013	7213 (14.16)	2297 (15.17)	1498 (5.62)		5279(15.96)	655(18.47)	716(9.27)	
2014	12600 (24.74)	4040 (26.67)	3803 (14.27)		8386(25.36)	1042(29.38)	1357(17.57)	
2015	9311 (18.28)	2596 (17.14)	3976 (14.92)		6400(19.35)	640(18.04)	1511(19.56)	
2016	8372 (16.44)	2681 (17.70)	4842 (18.16)		6104(18.46)	594(16.75)	1620(20.97)	
2017	6994 (13.73)	1998 (13.19)	5852 (21.95)		4237(12.81)	390(11)	1390(17.99)	
2018	6441 (12.65)	1534 (10.13)	6686 (25.08)		2661(8.05)	226(6.37)	1131(14.64)	
NEED VARIABLES								
MODE OF REVASCULARIZATION				**<.001**				**<.001**
PCI	43028 (84.48)	14825 (97.88)	26206(98.31)		28719(86.85)	3382(95.35)	7356(95.22)	
CABG	7414 (14.56)	299 (1.97)	398 (1.49)		4033(12.2)	156(4.4)	354(4.58)	
Fibrinolysis	489 (0.96)	22 (0.15)	53 (0.20)		315(0.95)	9(0.25)	15(0.19)	
TYPE OF STENTS				**0.0002**				**<.001**
DES	20174 (88.84)	7583 (90.41)	14297 (88.95)		12915(87.94)	1657(92.78)	3763(89.92)	
BMS	2533 (11.16)	804 (9.59)	1776 (11.05)		1771(12.06)	129(7.22)	422(10.08)	
TYPE OF ACS				**<.001**				**<.001**
NSTEMI/UA	19047 (64.05)	5555 (57.07)	10870 (56.69)		11302(72.8)	1151(66.57)	2878(63.88)	
STEMI	10692 (35.95)	4178 (42.93)	8303 (43.31)		4223(27.2)	578(33.43)	1627(36.12)	
CCI INDEX				**<.001**				**<.001**
0	16227 (31.86)	4881 (32.23)	7242 (27.17)		9246(27.96)	1154(32.53)	2080(26.93)	
1	19214 (37.73)	6257 (41.31)	11054 (41.47)		9894(29.92)	1205(33.97)	2413(31.24)	
2	8725 (17.13)	2551 (16.84)	5252 (19.70)		6106(18.47)	604(17.03)	1538(19.91)	

>=3	6765 (13.28)	1457 (9.62)	3109 (11.66)		7821(23.65)	584(16.46)	1694(21.93)	
ELIXHAUSER INDEX (READMISSION)				**<.001**				**<.001**
< 0	15161 (29.77)	4826 (31.86)	8928 (33.49)		8193(24.78)	1032(29.1)	2180(28.22)	
0	12439 (24.42)	4399 (29.04)	7110 (26.67)		5707(17.26)	721(20.33)	1492(19.31)	
1-5	3999 (7.85)	1061 (7.01)	2043 (7.66)		2373(7.18)	222(6.26)	559(7.24)	
6-13	11690 (22.95)	3283 (21.68)	5446 (20.43)		8122(24.56)	928(26.16)	1806(23.38)	
>=14	7642 (15.00)	1577 (10.41)	3130 (11.74)		8672(26.23)	644(18.16)	1688(21.85)	
ELIXHAUSER INDEX (MORTALITY)				**<.001**				**<.001**
< 0	27080 (53.17)	8215 (54.24)	14731 (55.26)		14864(44.95)	1880(53)	3783(48.97)	
0	13046 (25.62)	4552 (30.05)	7380 (27.69)		6219(18.81)	774(21.82)	1589(20.57)	
1-5	4823 (9.47)	1200 (7.92)	2183 (8.19)		4717(14.26)	388(10.94)	1040(13.46)	
6-13	4550 (8.93)	981 (6.48)	1885 (7.07)		5055(15.29)	380(10.71)	923(11.95)	
>=14	1432 (2.81)	198 (1.31)	478 (1.79)		2212(6.69)	125(3.52)	390(5.05)	
PATIENTS AT BLEEDING RISK (AHA CRITERIA)								
High-risk comorbid conditions in the past 6 months								
Diabetes	15310 (30.06)	4160 (27.47)	7121 (26.71)	**<.001**	10495(31.74)	1124(31.69)	2307(29.86)	**0.005**
Anemia	2400 (4.71)	391 (2.58)	836 (3.14)	**<.001**	2750(8.32)	171(4.82)	536(6.94)	**<.001**
Chronic Kidney Disease	2438 (4.79)	437 (2.89)	898 (3.37)	**<.001**	3558(10.76)	240(6.77)	731(9.46)	**<.001**
Low Body Weight	303 (0.59)	40 (0.26)	69 (0.26)	**<.001**	324(0.98)	13(0.37	49(0.63)	**<.001**
History of Prior Bleeding (six months): Intracranial, Gastrointestinal	5644 (11.08)	722 (4.77)	1449 (5.44)	**<.001**	4745(14.35)	295(8.32)	767(9.93)	**<.001**

bleeding, and other major bleeding)								
Concomitant use of high risk meds (oral anticoagulants, NSAIDS, and corticosteroids)	5407 (10.62)	987 (6.52)	1838 (6.89)	**<.001**	5432(16.73)	385(10.85)	801(10.37)	**<.001**
MEDICATION HISTORY IN THE PAST 6 MONTHS								
Cardiac Drugs								
Anticoagulants	2527 (4.96)	273 (1.80)	526 (1.97)	**<.001**	5196(15.71)	228(6.43)	586(7.59)	**<.001**
Antiplatelet drugs	8463 (16.62)	2534 (16.73)	3375 (12.66)	**<.001**	6995(21.15)	849(23.94)	1540(19.94)	
Antiarrhythmic drugs	748 (1.47)	120 (0.79)	152 (0.57)	**<.001**	1315(3.98)	91(2.57)	194(2.51)	**<.001**
Antihypertensive								
Ace Inhibitors	14237 (27.95)	3848 (25.40)	6215 (23.31)	**<.001**	10334(31.25)	1050(29.6)	2215(28.67)	
Angiotensin II antagonists	9214 (18.09)	2681 (17.70)	4615 (17.31)	**0.025**	8480(25.64)	917(25.85)	2011(26.03)	
Alpha-beta blockers	277 (0.54)	60 (0.40)	113 (0.42)	**0.016**	271(0.82)	22(0.62)	48(0.62)	0.11
Beta blockers	21232 (41.69)	5527 (36.49)	8355 (31.42)	**<.001**	19020(57.52)	1875(52.86)	3952(51.16)	**<.001**
Calcium channel blockers	9881 (19.40)	2537 (16.75)	4458 (16.72)	**<.001**	10450(31.6)	969(27.32)	2262(29.28)	**<.001**
Antidiabetics								
Miscellaneous (Biguanides, GLP-1 analogues DPP4, alpha-glucoside ihibitors, incretin mimetics, amylin analogues, glucagon, and combinations)	10197 (20.02)	2908 (19.19)	4759 (17.85)	**<.001**	6857(20.74)	805(22.7)	1657(21.45)	**0.014**
Meglitinides	132 (0.26)	29 (0.19)	45 (0.17)	**0.027**	209(0.63)	16(0.45)	44(0.57)	0.37

Sulfonylureas	4188 (8.22)	1060 (7.00)	1779 (6.67)	**<.001**	3661(11.07)	389(10.97)	816(10.56)	0.43
SGLT	1179 (2.31)	358 (2.36)	761 (2.85)	**<.001**	255(0.77)	41(1.16)	109(1.41)	**<.001**
TZD	657 (1.29)	192 (1.27)	306 (1.48)	0.23	556(1.68)	71(2)	110(1.42)	0.072
Diuretics								
Loop diuretics	3945 (7.75)	780 (1.50)	1182 (2.43)	**<.001**	6426(19.43)	469(13.22)	1054(13.64)	**<.001**
Potassium-sparing diuretics	1915 (3.75)	466 (3.08)	711 (2.67)	**<.001**	2051(6.2)	197(5.55)	391(5.06)	**0.0004**
Thiazide diuretics	3937 (7.73)	1031 (6.80)	1730 (6.49)	**<.001**	3544(10.72)	365(10.29)	791(10.24)	0.386
Carbonic anhydrase inhibitors	55 (0.11)	12 (0.08)	27 (0.10)	0.6208	58(0.18)	7(0.2)	22(0.28)	0.1476
Lipid lowering Agents	26793 (52.61)	7712 (50.92)	12035 (45.15)	**<.001**	21964(66.42)	2364(66.65)	4871(63.06)	**<.001**
Cardiac glycosides (Digoxin)	377 (0.74)	58 (0.38)	72 (0.27)	**<.001**	1013(3.06)	72(2.03)	130(1.68)	**<.001**
Estrogens	828 (1.63)	270 (1.78)	386 (1.45)	**0.025**	655(1.98)	67(1.89)	152(1.97)	0.93
Antidepressants	9820 (19.28)	2702 (17.84)	4625 (17.35)	**<.001**	6547(19.8)	674(19)	1390(17.99)	**0.001**
Antacids								
PPIs	9976 (19.59)	2910 (19.21)	4750 (17.81)	**<.001**	9363(28.32)	953(26.87)	2052(26.56)	**0.003**
H2RA	1484 (2.91)	372 (2.46)	680 (2.55)	**0.009**	1804(5.46)	174(4.91)	396(5.13)	0.23

Acronyms: CCAE: MarketScan Commercial Claims and Encounters database, MDCR: Medicare Supplemental and Coordination of Benefits (COB) Database, EPO: Exclusive Provider Organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; DES: drug-eluting stent; BMS: bare-metal stent; ACS: acute coronary syndrome; STEMI: ST wave elevated myocardial infarction; NSTEMI: Non-ST elevated myocardial infarction; UA: unstable angina; CCI: Charlson's comorbidity index; AHA: American Heart Association; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: Sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 3. 3 Prevalence of Prescription of Different P2Y12 Inhibitors:

MarketScan 2013-2018

P2Y12 inhibitors	2013	2014	2015	2016	2017	2018	Total
	CCAE SAMPLE (Age ≤65 Years) (N=92734)						
Clopidogrel (N)	7122	12618	9335	8384	7001	6471	50931
(%)	***65.47***	***61.69***	***58.66***	***52.68***	***47.15***	***43.95***	
Prasugrel (N)	2271	4045	2603	2685	2000	1542	15146
(%)	***20.88***	***19.78***	***16.36***	***16.87***	***13.47***	***10.47***	
Ticagrelor (N)	1485	3792	3975	4846	5847	6712	26657
(%)	***13.65***	***18.54***	***24.98***	***30.45***	***39.38***	***45.58***	
	MDCR SAMPLE (Age ≥65 Years) (N=44339)						
Clopidogrel (N)	5279	8386	6400	6104	4237	2661	33067
(%)	***79.38***	***77.76***	***74.85***	***73.38***	***70.42***	***66.23***	
Prasugrel (N)	655	1042	640	594	390	226	3547
(%)	***9.85***	***9.66***	***7.48***	***7.14***	***6.48***	***5.62***	
Ticagrelor (N)	716	1357	1511	1620	1390	1131	716
(%)	***10.77***	***12.58***	***17.67***	***19.48***	***23.1***	***28.15***	

Acronym: P2Y12 inhibitors: adenosine diphosphate (ADP) receptor antagonists, CCAE: MarketScan Commercial Claims and Encounters database, MDCR: Medicare Supplemental and coordination of benefits (COB) Database

Appendix Table 3. 4 Prevalence of P2Y12 Inhibitors as Per the Technique of Revascularization in the CCAE Sample (Age ≤65 Years): MarketScan 2013-2018

CCAE Sample (N=92,734)							
P2Y12 inhibitors	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**Total**
PCI (N=84,059)							
Clopidogrel (N)	6076	10591	7836	7224	5895	5406	43028
(%)	***62.20***	***58.00***	***54.84***	***49.44***	***43.29***	***40.00***	
Prasugrel (N)	2235	3949	2552	2622	1955	1512	14825
(%)	***22.88***	***21.63***	***17.86***	***17.95***	***14.36***	***11.19***	
Ticagrelor (N)	1458	3720	3901	4765	5766	6596	26206
(%)	***14.92***	***20.37***	***27.30***	***32.61***	***42.35***	***48.81***	
CABG (N=8,111)							
Clopidogrel (N)	958	1838	1353	1136	1082	1047	7414
(%)	***94.29***	***92.27***	***92.29***	***90.09***	***90.7***	***88.5***	
Prasugrel (N)	34	92	45	59	40	29	299
(%)	***3.35***	***4.62***	***3.07***	***4.68***	***3.35***	***2.45***	
Ticagrelor (N)	24	62	68	66	71	107	107
(%)	***2.36***	***3.11***	***4.64***	***5.23***	***5.95***	***9.04***	
FIBRINOLYSIS (N=564)							
Clopidogrel (N)	88	189	146	24	24	18	489
(%)	***94.62***	***93.1***	***92.41***	***55.81***	***61.54***	***64.29***	
Prasugrel (N)	2	4	6	4	5	1	22
(%)	***2.15***	***1.97***	***3.8***	***9.3***	***12.82***	***3.57***	
Ticagrelor (N)	3	10	6	15	10	9	53
(%)	***3.23***	***4.93***	***3.8***	***34.88***	***25.64***	***32.14***	

Acronym: P2Y12 inhibitors: adenosine diphosphate (ADP) receptor antagonists; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting, CCAE: MarketScan Commercial Claims and Encounters Database.

Appendix Table 3. 5 Prevalence of P2Y12 Inhibitors as Per the Technique of Revascularization in the MDCR Sample (Age ≥65 Years): MarketScan 2013-2018

MDCR sample (N=44,339)							
P2Y12 inhibitors	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**Total**
PCI (N=39457)							
Clopidogrel (N)	4552	7206	5529	5323	3755	2354	28719
(%)	***77.79***	***75.76***	***72.97***	***71.75***	***68.87***	***64.56***	
Prasugrel (N)	624	1000	612	568	360	218	3382
(%)	***10.66***	***10.51***	***8.08***	***7.66***	***6.6***	***5.98***	
Ticagrelor (N)	676	1305	1436	1528	1337	1074	7356
(%)	***11.55***	***13.72***	***18.95***	***20.6***	***24.52***	***29.46***	
CABG (N=4,543)							
Clopidogrel (N)	651	1066	786	755	472	303	4033
(%)	***90.92***	***92.13***	***88.81***	***87.08***	***85.82***	***82.34***	
Prasugrel (N)	27	41	27	23	30	8	156
(%)	***3.77***	***3.54***	***3.05***	***2.65***	***5.45***	***2.17***	
Ticagrelor (N)	38	50	72	89	48	57	354
(%)	***5.31***	***4.32***	***8.14***	***10.27***	***8.73***	***15.49***	
FIBRINOLYSIS (N=339)							
Clopidogrel (N)	76	114	85	26	10	4	315
(%)	***92.68***	***97.44***	***95.51***	***81.25***	***66.67***	***100***	
Prasugrel (N)	4	1	1	3	0	0	9
(%)	***4.88***	***0.85***	***1.12***	***9.38***	***0***	***0***	
Ticagrelor (N)	2	2	3	3	5	0	15
(%)	***2.44***	***1.71***	***3.37***	***9.38***	***33.33***	***0***	

Acronym: P2Y12 inhibitors: adenosine diphosphate (ADP) receptor antagonists; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting, MDCR: Medicare Supplemental and coordination of benefits (COB) Database

Appendix Table 3. 6 Prevalence of P2Y12 Inhibitors among Patients with High Bleeding Risk in CCAE (Age ≤65 Years) and MDCR (Age ≥65 Years) Sample: MarketScan 2013-2018

P2Y12 Inhibitors	2013	2014	2015	2016	2017	2018	Total
	CCAE Sample (N=38146)						
Clopidogrel (N)	2843	5417	4234	3827	3420	3218	22959
(%)	***70.55***	***66.33***	***63.81***	***57.74***	***54.05***	***50.61***	
Prasugrel (N)	705	1416	973	1037	765	593	5489
(%)	***17.49***	***17.34***	***14.66***	***15.65***	***12.09***	***9.33***	
Ticagrelor (N)	482	1334	1428	1764	2143	2547	9698
(%)	***11.96***	***16.33***	***21.52***	***26.61***	***33.87***	***40.06***	
	MDCR Sample (N=23328)						
Clopidogrel (N)	2675	4391	3548	3481	2543	1468	18106
(%)	***82.18***	***80.23***	***78.22***	***75.87***	***74.55***	***71.09***	
Prasugrel (N)	268	492	290	286	185	111	1632
(%)	***8.23***	***8.99***	***6.39***	***6.23***	***5.42***	***5.38***	
Ticagrelor (N)	312	590	698	821	683	486	3590
(%)	***9.59***	***10.78***	***15.39***	***17.89***	***20.02***	***23.54***	

Acronym: P2Y12 inhibitors: adenosine diphosphate (ADP) receptor antagonists, CCAE: MarketScan Commercial Claims and Encounters database, MDCR: Medicare Supplemental and coordination of benefits (COB) Database

Appendix Table 3. 7 Prevalence of P2Y12 Inhibitors among the Patients with a History of Stroke or Trans Ischemic Events in CCAE (Age ≤65 Years) and MDCR (Age ≥65 Years) Sample: MarketScan 2013-2018

P2Y12 Inhibitor	CCAE sample (Total= 2721)		MDCR sample (Total=2600)	
	Number of patients	*Percentage*	*Number of patients*	*Percentage*
Clopidogrel	2118	77.84	2207	84.88
Prasugrel	207	7.61	135	5.19
Ticagrelor	396	14.55	258	9.92

Acronym: P2Y12 inhibitors: adenosine diphosphate (ADP) receptor antagonists, CCAE: MarketScan Commercial Claims and Encounters database, MDCR: Medicare Supplemental and coordination of benefits (COB) database

Appendix Table 3. 8 Trend of P2Y12 Inhibitors over Time by a Quarter in the CCAE Sample (Age ≤65 Years): MarketScan 2013-2018

Year (Quarter)	Clopidogrel		Prasugrel		Ticagrelor		Total	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
2013 (Quarter 3)	3,546	65.59	1,176	21.75	684	12.65	5,406	5.83
2013 (Quarter 4)	3,576	65.35	1,095	20.01	801	14.64	5,472	5.90
2014(Quarter 1)	2,884	63.61	973	21.46	677	14.93	4,534	4.89
2014 (Quarter2)	3,058	62.09	1,018	20.67	849	17.24	4,925	5.31
2014 (Quarter3)	3,371	61.18	1,061	19.26	1,078	19.56	5,510	5.94
2014 (Quarter 4)	3,305	60.24	993	18.10	1,188	21.66	5,486	5.92
2015 (Quarter 1)	2,303	59.97	680	17.71	857	22.32	3,840	4.14
2015 (Quarter 2)	2,344	60.62	581	15.02	942	24.36	3,867	4.17
2015 (Quarter 3)	2,374	57.93	632	15.42	1,092	26.65	4,098	4.42
2015 (Quarter 4)	2,314	56.33	710	17.28	1,084	26.39	4,108	4.43
2016 (Quarter 1)	2,019	54.22	682	18.31	1,023	27.47	3,724	4.02
2016 (Quarter2)	2,000	52.00	635	16.51	1,211	31.49	3,846	4.15
2016 (Quarter 3)	2,164	53.18	657	16.15	1,248	30.67	4,069	4.39
2016 (Quarter 4)	2,201	51.47	711	16.63	1,364	31.9	4,276	4.61
2017 (Quarter 1)	1,632	48.64	506	15.08	1,217	36.27	3,355	3.62
2017 (Quarter 2)	1,719	47.80	517	14.38	1,360	37.82	3,596	3.88
2017 (Quarter 3)	1,884	47.37	517	13.00	1,576	39.63	3,977	4.29
2017 (Quarter 4)	1,766	45.05	460	11.73	1,694	43.21	3,920	4.23
2018 (Quarter 1)	1,400	44.46	365	11.59	1,384	43.95	3,149	3.40
2018 (Quarter 2)	1,506	44.36	390	11.49	1,499	44.15	3,395	3.66
2018 (Quarter 3)	1,776	43.56	416	10.20	1,885	46.23	4,077	4.40
2018 (Quarter 4)	1,789	43.59	371	9.04	1,944	47.37	4,104	4.43
Total	50,931		15,146		26,657		92,734	100

Acronyms: CCAE: MarketScan Commercial Claims and Encounters Database.

Test of trend (For Appendix Table 3.8)

Cochran-Armitage Trend Test (Clopidogrel)	
Statistic (Z)	45.65
One-sided Pr > Z	<.0001
Two-sided Pr > |Z|	<.0001

Cochran-Armitage Trend Test (Prasugrel)	
Statistic (Z)	28.27
One-sided Pr > Z	<.0001
Two-sided Pr > |Z|	<.0001

Cochran-Armitage Trend Test (Ticagrelor)	
Statistic (Z)	-73.28
One-sided Pr < Z	<.0001
Two-sided Pr > |Z|	<.0001

Appendix Table 3. 9 Trend of P2Y12 Inhibitors over Time by a Quarter in the MDCR Sample (Age ≥65 Years) Sample: MarketScan 2013-2018

Year (Quarter)	Clopidogrel		Prasugrel		Ticagrelor		Total	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
2013 (Quarter 3)	2,558	79.66	327	10.18	326	10.15	3,211	7.24
2013 (Quarter 4)	2,721	79.12	328	9.54	390	11.34	3,439	7.76
2014 (Quarter 1)	1,995	79.17	266	10.56	259	10.28	2,520	5.68
2014 (Quarter 2)	2,114	78.12	242	8.94	350	12.93	2,706	6.1
2014 (Quarter 3)	2,084	76.65	267	9.82	368	13.53	2,719	6.13
2014 (Quarter 4)	2,193	77.22	267	9.4	380	13.38	2,840	6.41
2015 (Quarter1)	1,520	75.1	148	7.31	356	17.59	2,024	4.56
2015 (Quarter 2)	1,605	74.55	171	7.94	377	17.51	2,153	4.86
2015 (Quarter 3)	1,635	75.94	145	6.73	373	17.32	2,153	4.86
2015 (Quarter 4)	1,640	73.84	176	7.92	405	18.24	2,221	5.01
2016 (Quarter 1)	1,479	73.8	145	7.24	380	18.96	2,004	4.52
2016 (Quarter 2)	1,561	73.22	165	7.74	406	19.04	2,132	4.81
2016 (Quarter 3)	1,467	73.61	132	6.62	394	19.77	1,993	4.49
2016 (Quarter 4)	1,597	72.96	152	6.94	440	20.1	2,189	4.94
2017 (Quarter 1)	1,074	70.43	107	7.02	344	22.56	1,525	3.44
2017 (Quarter 2)	1,052	71.08	82	5.54	346	23.38	1,480	3.34
2017 (Quarter 3)	1,074	72.47	101	6.82	307	20.72	1,482	3.34
2017 (Quarter 4)	1,037	67.78	100	6.54	393	25.69	1,530	3.45
2018 (Quarter 1)	579	65.8	45	5.11	256	29.09	880	1.98
2018 (Quarter 2)	602	64.8	61	6.57	266	28.63	929	2.1
2018 (Quarter 3)	677	68.52	53	5.36	258	26.11	988	2.23
2018 (Quarter 4)	803	65.77	67	5.49	351	28.75	1,221	2.75
Total	33,067		3,547		7,725		44,339	100

Acronyms: MDCR: Medicare Supplemental and coordination of benefits (COB) database

Test of trend (For Appendix Table 3.9):

Cochran-Armitage Trend Test (Clopidogrel)	
Statistic (Z)	18.5276
One-sided Pr > Z	<.0001
Two-sided Pr > |Z|	<.0001

Cochran-Armitage Trend Test (Prasugrel)	
Statistic (Z)	11.0425
One-sided Pr > Z	<.0001
Two-sided Pr > |Z|	<.0001

Cochran-Armitage Trend Test (Ticagrelor)	
Statistic (Z)	-29.1668
One-sided Pr < Z	<.0001
Two-sided Pr > |Z|	<.0001

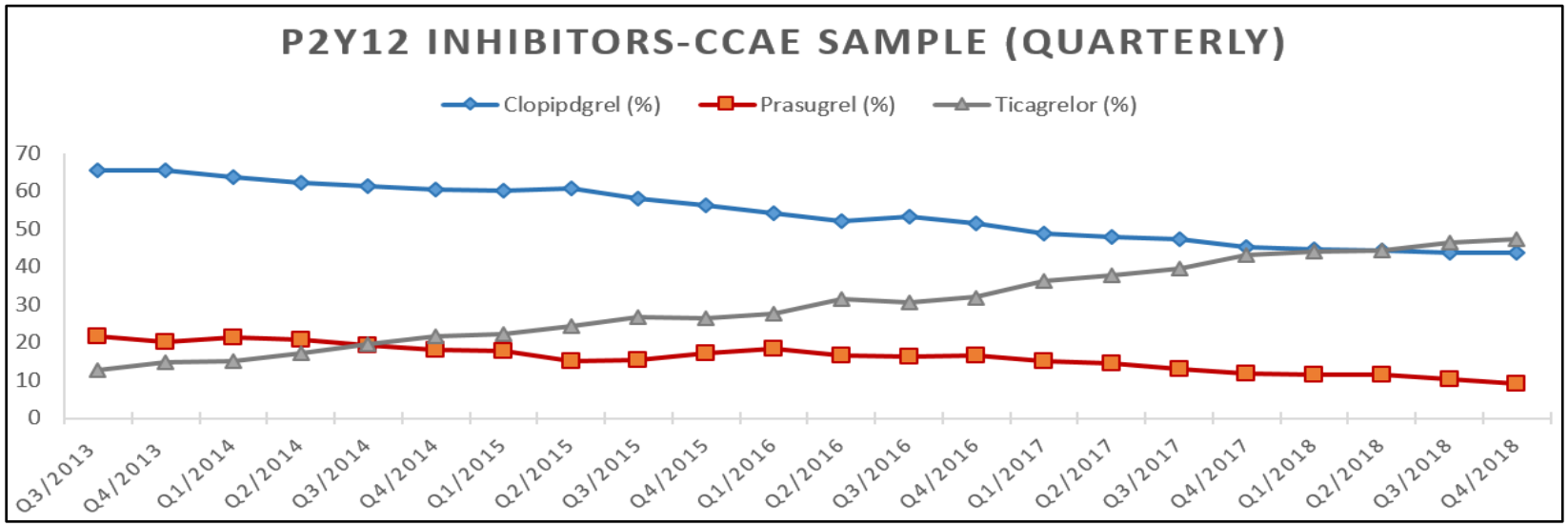
Appendix Table 3. 10 Comorbid Conditions in the Past 6 Months in the CCAE Sample (Age ≤65 Years): MarketScan 2013-2018

S. No.	Elixhauser Condition	Clopidogrel (N=50,931)	Prasugrel (15,146)	Ticagrelor (26,657)
1.	Acquired immune deficiency syndrome (AIDS)	107 (0.21%)	28 (0.18%)	32 (0.12%)
2.	Alcohol abuse	542 (1.06%)	119 (0.79%)	264 (0.99%)
3.	Chronic blood loss anemia	130 (0.26%)	31 (0.20%)	59 (0.22%)
4.	Chronic pulmonary disease	2,925 (5.74%)	699 (4.62%)	1,248 (4.68%)
5.	Coagulopathy	905 (1.78%)	110 (0.73%)	217 (0.81%)
6.	Congestive heart failure	3,435 (6.74%)	718 (4.74%)	1,515 (5.68%)
7.	Deficiency anemias	2,038 (4.00%)	373 (2.46%)	745 (2.79%)
8.	Depression	1,619 (3.18%)	390 (2.57%)	771 (2.89%)
9.	Diabetes w/o chronic complications	11,445 (22.47%)	3,158 (20.85%)	5,168 (19.39%)
10.	Diabetes with chronic complications	3,865 (7.59%)	888 (5.86%)	1,974 (7.41%)
11.	Drug abuse	174 (0.34%)	40 (0.26%)	87 (0.33%)
12.	Fluid and electrolyte disorders	2,800 (5.50%)	591 (3.90%)	1,184 (4.44%)
13.	Hypothyroidism	2,355 (4.62%)	651 (4.30%)	1,241 (4.66%)
14.	Liver disease	670 (1.32%)	152 (1.00%)	241 (0.90%)
15.	Lymphoma	147 (0.29%)	22 (0.15%)	59 (0.22%)
16.	Metastatic cancer	143 (0.28%)	17 (0.11%)	40 (0.15%)
17.	Obesity	6,841 (13.43%)	1,846 (12.19%)	3,735 (14.01%)
18.	Other neurological disorders	715 (1.40%)	166 (1.10%)	335 (1.26%)
19.	Paralysis	203 (0.40%)	17 (0.11%)	43 (0.16%)
20.	Peptic ulcer disease x bleeding	51 (0.10%)	15 (0.10%)	33 (0.12%)
21.	Peripheral vascular disease	2,787 (5.47%)	615 (4.06%)	1,089 (4.09%)
22.	Psychoses	359 (0.70%)	88 (0.58%)	129 (0.48%)
23.	Pulmonary circulation disease	404 (0.79%)	75 (0.50%)	105 (0.39%)
24.	Renal failure	1,778 (3.49%)	299 (1.97%)	642 (2.41%)
25.	Rheumatoid arthritis/collagen vas	405 (0.80%)	105 (0.69%)	205 (0.77%)
26.	Solid tumor w/out metastasis	521 (1.02%)	101 (0.67%)	217 (0.81%)
27.	Valvular disease	3,058 (6.00%)	720 (4.75%)	1,107 (4.15%)
28.	Weight loss	227 (0.45%)	30 (0.20%)	73 (0.27%)
29.	hypertension	32,174 (63.17%)	9,089 (60.01%)	16,636 (62.41%)

Appendix Table 3. 11 Comorbid Conditions in the Past 6 Months in the MDCR Sample (Age ≥65 Years): MarketScan 2013-2018

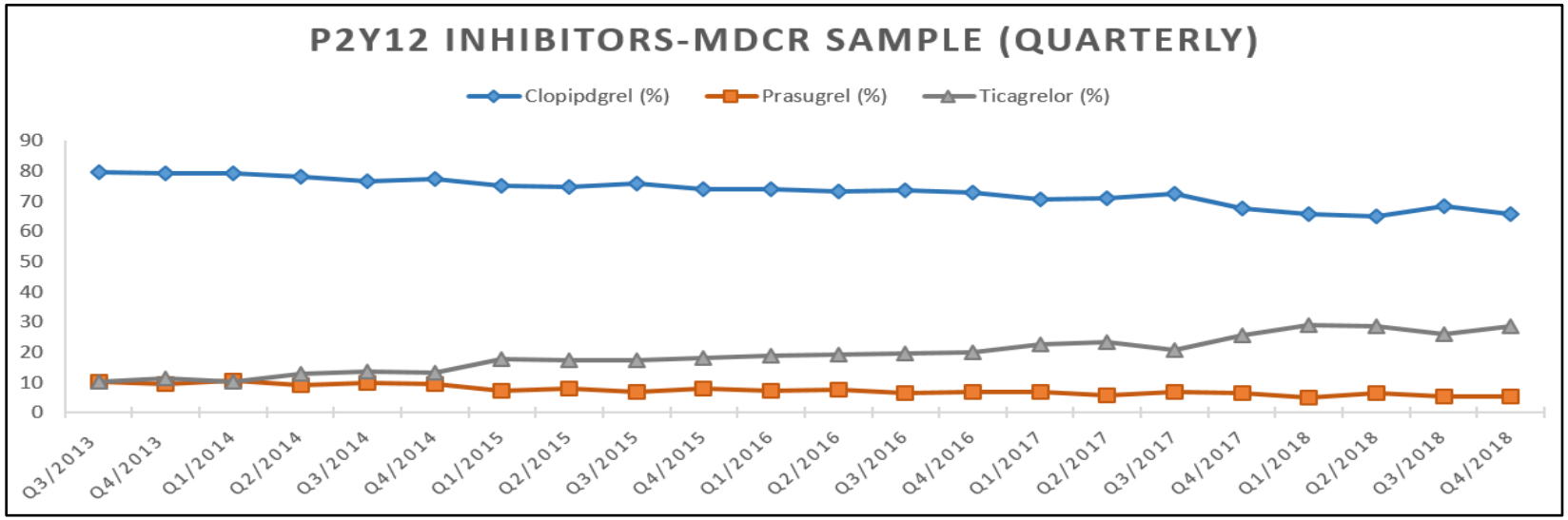
S. No.	Elixhauser Condition	Clopidogrel (N=33,067)	Prasugrel (N=3,547)	Ticagrelor (N=7,725)
1.	Acquired immune deficiency syndrome (AIDS)	11 (0.03%)	1 (0.03%)	4 (0.05%)
2.	Alcohol abuse	137 (0.41%)	13 (0.37%)	36 (0.47%)
3.	Chronic blood loss anemia	205 (0.62%)	18 (0.51%)	31 (0.40%)
4.	Chronic pulmonary disease	3,456 (10.45%)	274 (7.72%)	732 (9.48%)
5.	Coagulopathy	784 (2.37%)	47 (1.33%)	117 (1.51%)
6.	Congestive heart failure	4,787 (14.48%)	350 (9.87%)	897 (11.61%)
7.	Deficiency Anemias	2,564 (7.75%)	174 (4.91%)	514 (6.65%)
8.	Depression	897 (2.71%)	77 (2.17%)	209 (2.71%)
9.	Diabetes w/o chronic complications	8,209 (24.83%)	919 (25.91%)	1,736 (22.47%)
10.	Diabetes with chronic complications	2,594 (7.84%)	254 (7.16%)	619 (8.01%)
11.	Drug abuse	45 (0.14%)	3 (0.08%)	10 (0.13%)
12.	Fluid and electrolyte disorders	2,396 (7.25%)	170 (4.79%)	447 (5.79%)
13.	Hypothyroidism	2,739 (8.28%)	243 (6.85%)	610 (7.90%)
14.	Liver disease	239 (0.72%)	17 (0.48%)	47 (0.61%)
15.	Lymphoma	163 (0.49%)	11 (0.31%)	32 (0.41%)
16.	Metastatic cancer	143 (0.43%)	7 (0.20%)	37 (0.48%)
17.	Obesity	2,658 (8.04%)	317 (8.94%)	651 (8.43%)
18.	Other neurological disorders	993 (3.00%)	64 (1.80%)	218 (2.82%)
19.	Paralysis	186 (0.56%)	7 (0.20%)	25 (0.32%)
20.	Peptic ulcer Disease x bleeding	60 (0.18%)	5 (0.14%)	20 (0.26%)
21.	Peripheral vascular disease	3,445 (10.42%)	267 (7.53%)	665 (8.61%)
22.	Psychoses	198 (0.60%)	17 (0.48%)	36 (0.47%)
23.	Pulmonary circulation disease	674 (2.04%)	44 (1.24%)	70 (0.91%)
24.	Renal failure	2,677 (8.10%)	171 (4.82%)	504 (6.52%)
25.	Rheumatoid arthritis/collagen vas	359 (1.09%)	34 (0.96%)	72 (0.93%)
26.	Solid tumor w/out metastasis	960 (2.90%)	49 (1.38%)	176 (2.28%)
27.	Valvular disease	4,974 (15.04%)	373 (10.52%)	904 (11.70%)
28.	Weight loss	266 (0.80%)	14 (0.39%)	58 (0.75%)
29.	hypertension	23,498 (71.06%)	2,460 (69.35%)	5,354 (69.31%)

Appendix Figure 3. 1 Trend of P2Y12 Inhibitors in CCAE Sample (Age ≤65 Years): MarketScan 2013-2018



Acronyms: P2Y12 inhibitors: adenosine diphosphate (ADP) receptor antagonists; Q: quarter, CCAE: MarketScan Commercial Claims and Encounters database

Appendix Figure 3. 2 Trend of P2Y12 Inhibitors in the MDCR Sample (Age ≥65 Years): MarketScan 2013-2018



Acronyms: P2Y12 inhibitors: adenosine diphosphate (ADP) receptor antagonists; Q: quarter, MDCR: Medicare Supplemental and coordination of benefits (COB) database

3.6.4. Supplementary Results

The following section describes the prescription pattern and predictors of P2Y12 inhibitors use based on all the variables we studied using Andersen's Behaviors of Healthcare Utilization in great detail. This section covers the P2Y12 inhibitors use for both CCAE and MDCR samples that couldn't be included in the main manuscript.

(A) DESCRIPTION OF PRESCRIPTION PATTERN OF DIFFERENT P2Y12 INHIBITORS:

We identified 92,734 and 44,339 patients with CHD who were revascularized after a CHD event in CCAE and MDCR samples, respectively. The baseline characteristics as per the P2Y12 inhibitor prescribed for both of the study samples (i.e., CCAE & MDCR are described in **Appendix Table 3.2**. All the comparisons made in the baseline variables were statistically significant at p=0.05.

(1.1) Difference in P2Y12 inhibitors based on the patients' characteristics:

We looked at the difference in the prescribing of P2Y12 inhibitors based on the patients' characteristics identified using Andersen's behavior model as follows:

a. Predisposing demographic variables

In the exploratory analysis, for the predisposing demographic variables, in the CCAE sample **(Appendix Table 3.2)**, we had 50,931, 15,146, and 26,657 patients who filled clopidogrel, prasugrel, and ticagrelor for secondary CHD prophylaxis, respectively**.** Similarly, we had 33,697, 3,664, and 7,895 (clopidogrel, prasugrel, and ticagrelor) patients for the MDCR sample **(Appendix Table 3.2)**.

(i) Age of the population: Patients with higher age were more likely to have filled clopidogrel compared to prasugrel and ticagrelor (60.7% vs 54.9%, and 54.9%). Decreasing age in this sample was associated with lower prescription of clopidogrel over newer P2Y12 inhibitors for the following age groups: 46-55 years (31.3% vs 34.8% and 34.8%), 36-45 years (7.3% vs 9.3% and 9.2%), and age group 26-35 years (0.6% vs 0.9 and 1.0%). The majority of patients who were revascularized in the CCAE study sample came from the 56-65 years category i.e., 60.7%, 54.9%, and 54.9% corresponding to clopidogrel, prasugrel, and ticagrelor respectively. Likewise, for the MDCR sample, a majority of the patients came from the 65-74 age group followed by 75-84 years and above 85 years groups. For the MDCR sample, increasing age was linked to greater clopidogrel prescription fill compared to newer P2Y12 inhibitors. In this study sample, 75-84 years age group filled more clopidogrel for the years 2013 to 2018 (39.6% vs 21.0% and 35.7%). Similar patterns were seen among the patients who were 85 years and older (12.0% vs 2.9% and 7.4%). Additionally, similar to CCAE data, decreasing age was linked to lower clopidogrel prescription compared to prasugrel and ticagrelor respectively (48.4% vs 76.1 and 56.9%).

(ii) Gender of the population: In both of the study samples, the majority of patients were males compared to their counterparts. In the CCAE sample, a higher percentage of males filled prasugrel compared to clopidogrel and ticagrelor (79.4% vs 75.7% and 77.3%). Similarly in the MDCR sample, a higher percentage of males were prescribed with prasugrel compared to clopidogrel and ticagrelor (72.3% vs 65.9% and 66.0%).

(iii) Region to which patients belong: We observed interesting patterns in P2Y12 prescribing as it varied substantially with the geographical region in the US. For the

CCAE data, in the Northeast region, we observed that ticagrelor was prescribed greater compared to clopidogrel and prasugrel (18.6% vs 16.9% and 15.3%). And for the Northcentral region, clopidogrel was filled more frequently compared to other agents. Importantly, in the South region, newer agents were prescribed more often. For example, prasugrel (51.8%) and ticagrelor (47.1%) prescriptions were higher compared to clopidogrel (45.1%). Nevertheless, in the West region, clopidogrel was the most prescribed P2Y12 inhibitor. It should be noted that we had an over-representation of the patients from the Southern region which made up to 45%-51% of all prescription fills for all the P2Y12 inhibitors in this study. We continued to observe a variation in the P2Y12 inhibitors prescription by region in the MDCR sample as well. For the Northeast region, ticagrelor appeared to more likely the choice of P2Y12 inhibitor compared to clopidogrel and prasugrel (24.0 vs 21.9% and 22.7%). Similarly, in the South region, prasugrel was prescribed more frequently (36.4% vs 31.9% and 33.4%). However, in the Northeast region, ticagrelor was prescribed more compared to prasugrel and clopidogrel (24.0% vs 22.7% and 21.9%).

b. Enabling variables

(i) Insurance plan type: Regarding enabling variables, among the CCAE sample, the majority of patients had PPO plans followed by HMO and CDHP plans. Among patients with PPO plans, prasugrel was prescribed more compared to clopidogrel and ticagrelor (59.1% vs 57.5% and 57.2%). In HMO plans, interestingly, clopidogrel fill was higher compared to prasugrel and ticagrelor (10.3% vs 8.9% and 9.3%). Additionally, among CDHP plans, clopidogrel was least filled and ticagrelor was filled greater than prasugrel and clopidogrel i.e., 12.2% vs 10.5% and 10.0%, respectively. On the other hand, in the

MDCR sample, a majority of patients were enrolled in comprehensive and PPO plans. Patients with comprehensive plans were more likely to fill clopidogrel compared to prasugrel and ticagrelor (39.3% vs 35.7% and 38.7%). However, PPO plans were linked to a higher prescription of newer agents. For instance, prasugrel was prescribed more compared to clopidogrel and ticagrelor (46.4% vs 42.7% and 43.4%) in PPO plans.

(ii) Index year of P2Y12 inhibitor prescription: For the index year, with an increment of year, the use of clopidogrel share decreased with time e.g. 24.7% in 2014 to 12.7% in 2018. Similarly, prasugrel fill also decreased from 26.7% to 10.1% during the same years. Nevertheless, the ticagrelor prescription fill increased over time from 14.3% to 25.1% from the year 2014 to 2018. It is interesting to note that in 2014, prasugrel was fill was higher compared to clopidogrel and ticagrelor (26.7% vs 24.7% and 14.3%); however, by the year 2018, a significant shift was observed in the P2Y12 prescribing as ticagrelor was prescribed more compared to clopidogrel and prasugrel i.e., 25.1% vs 12.7% and 10.1%, respectively. On the other hand, in the MDCR sample, similar patterns were seen in the prescription fill of clopidogrel and prasugrel. However, for ticagrelor, the prescription fill increased from the year 2014 to 2016 (17.6% to 21.0%) and then decreased to 14.6% in 2018.

c. Need variables

(i) Type of revascularization*:* Among the potential need variables, for the CCAE sample, we observed that if revascularized with PCI, patients were more likely to fill newer agents. For example, ticagrelor (98.3%) and prasugrel (97.9%) were filled more frequently compared to clopidogrel (84.5%). Interestingly, among patients revascularized

using CABG, clopidogrel was the most prescribed drug. We observed similar patterns in the MDCR population as well.

(ii) Type of stent: For the type of stent used in PCI, newer agents were preferred over clopidogrel in both of the study samples if DES were utilized. However, clopidogrel was preferred over other agents if revascularized using BMS.

(iii) Type of ACS presentation: We further looked at the prescription as per the presentation of ACS whether NSTEMI/UA or STEMI. We observed that for the NSTEMI/UA presentation, clopidogrel was utilized greater (64.1%) over prasugrel (57.1%) and ticagrelor (56.7%). However, for STEMI, newer agents, prasugrel (42.9%) and ticagrelor (43.3%) opted over clopidogrel (36.0%). We continued to see a similar pattern in the MDCR sample as well.

(iv) Comorbidities in the past 6 months: For the comorbidities as a potential need variable, we looked at the Charlson comorbidity index (CCI) and Elixhauser (EI) index if any difference in the prescribing of P2Y12 agents existed based on underlying conditions in the past six months. We saw that among the patients with a higher comorbidities index, for the CCAE data, we observed a higher prevalence of clopidogrel prescription compared to other agents. For example, among patients with CCI >=3 in commercially insured patients, clopidogrel was filled more often compared to P2Y12 agents. Similarly, clopidogrel (23.7%) was prescribed more frequently compared to prasugrel (16.5%) and ticagrelor (21.9%) in the MDCR sample as well. We observed a higher prevalence of newer agents compared to ticagrelor if patients had CCI =1 or less for both of the study samples. For EI comorbidities, we presented the prescription share using two different indexes (i) EI readmission index and (ii) EI mortality index. For the EI

readmission index, we observed a similar pattern as seen in the CCI index as we continue to observe higher newer agents' prescriptions among patients with lower EI index for readmission (e.g., EJ<0, EI=0) for both of the populations in this study. Additionally, we observed higher clopidogrel prescriptions with an increasing EI readmission index in both of the populations. For example, among patients with an EI readmission index of 14 or greater, the prevalence of clopidogrel was higher compared to prasugrel and ticagrelor (i.e., Commercial sample: 15.0% vs 10.4% vs 11.7% & Medicare sample: 26.2% vs 18.2% and 21.9%). For the EI mortality index, the majority of patients in this sample had an EI mortality index of less than zero and we found a similar pattern as observed in CCI and EI readmission indexes. Among patients with an EI mortality index of zero or less, newer agents were preferred over clopidogrel. However, an increase in the EI mortality index was associated with a higher prevalence of clopidogrel prescription over other agents for both sample populations. We also presented the comorbid conditions both populations were suffering in the past 6 months in **Appendix Tables 3.10 & 3.11.**

(v) High bleeding risk: We also observed high bleeding risk as a likely need variable and explored further if there was any difference between the prescribing of P2Y12 inhibitors. In CCAE and MDCR sample, among patients with diabetes as a high bleeding risk, the prevalence of clopidogrel fill was higher compared to prasugrel and ticagrelor (30.1% vs 27.5% and 26.7%; p<0.01), and (31.7% vs 31.7% and 29.9%; p<0.01), respectively. Similarly, for other comorbidities as high bleeding risk (i.e., anemia, chronic kidney disease, and low body weight), clopidogrel prescription was filled significantly higher than prasugrel and ticagrelor at p=0.05 in both of the sample populations. Other conditions we looked at for the high bleeding risks were any history of major bleeding in

the past 6 months (IC, GI, and any other major bleeding) and concomitant use of any of the high-risk medications (i.e. anticoagulants, Rx NSAIDs, or oral corticosteroids). Among patients with concomitant use of high-risk medications, clopidogrel prescription fill was significantly higher compared to prasugrel and ticagrelor (10.6% vs 6.5% and 6.9%; p<0.01) in the CCAE sample, and similar pattern were seen in the MDCR sample as well (i.e., 16.7 vs 10.9% and 10.4%; p=0.01). And among those with a history of prior major bleeding in the CCAE sample, clopidogrel was the choice of drug (11.1% vs 4.8% and 5.4%; p<0.01) and likewise in the MDCR sample (14.4% vs 8.3% and 9.9%; p<0.01).

(vi) Medication history in the past 6 months: We further looked at the medication history in the past 6 months related to the cardiovascular system as a possible need factor. In the CCAE sample, patients with a history of anticoagulants use were more likely to initiate clopidogrel compared to prasugrel and ticagrelor (5.0% vs 1.8% and 2.0%; <0.01) and similarly in the Medicare sample (15.7% vs 6.4% and 7.6%; p<0.01). Importantly, patients in the commercially claim sample with antiplatelet use in the past were more likely to initiate prasugrel (16.7%) compared to clopidogrel (16.6%) and ticagrelor (12.7%) and the difference was statistically significant at p=0.05. And for the MDCR sample, we observed a similar inclination towards prasugrel compared to clopidogrel and ticagrelor (23.9% vs 21.2% and 19.9%; p<0.01). This pattern could be potentially due to the higher need for more potent drugs maybe because of the treatment failure in the past. We further looked at anti-arrhythmic drugs in commercially insured patients and found that clopidogrel share was more than prasugrel and ticagrelor (1.5% vs 0.8% and 0.6%; p<0.01) and likewise for the Medicare population. For both of the sample populations, clopidogrel was the most prevalent medication prescribed among all

the past users of antihypertensive medications regardless of the therapeutic class of antihypertensives. These differences were statistically significant at p=0.05 except for the alpha-beta blockers in the MDCR population. We observed that for the antidiabetic medications, other than Sodium-glucose co-transporter inhibitors (SGLT) and thiazolidinediones (TZDs), clopidogrel was the choice of drug and the difference in the prevalence of prescription was statistically significant at p=0.05 in CCAE data. For SGLT users, ticagrelor was filled more often compared to clopidogrel and prasugrel (2.9% vs 2.3% and 2.4%; p<0.01). However, for the TZDs users, although ticagrelor was the most filled drug, the difference was not significant at p=0.05. Although for the MDCR sample, we observed significant differences only for miscellaneous and SGLT classes of antidiabetic drug users. Additionally, newer drugs were filled more often compared to clopidogrel for these groups. Regarding diuretics, we found that for both of the study samples clopidogrel was the most prevalent drug which was filled in the pharmacies. Other than the thiazide diuretics users in the MDCR sample, the differences in P2Y12 prevalence were statistically significant for all the diuretic categories at p=0.05. Among patients with a history of lipid-lowering agents, clopidogrel was the most prevalent drug compared to prasugrel and ticagrelor (52.6% vs 50.9% and 45.2%; p<0.01) for the CCAE sample. On the other hand, for the Medicare sample, prasugrel (66.65%) was the most prevalent medication filled followed by clopidogrel (66.4%) and ticagrelor (63.0%) and the difference in these group was statistically significant at p=0.05. Lastly, for the cardiac glycosides, antidepressants, antacids, for both of the samples, clopidogrel was the most frequently filled drug compared to newer drugs, and we observed the statistically significant differences in the P2Y12 prescription fill for these drug classes at p=0.05 except for the H2 receptor antagonists in MDCR sample.

(1.2) Difference in the prescription of different P2Y12 inhibitors from the year 2013 to 2018:

We looked at the difference in the annual prevalence of P2Y12 inhibitors from the year 2013 to 2018. For the CCAE **(Appendix Table 3.3)**, from the year 2013 to 2018, the prevalence of prescription for clopidogrel was found to be decreasing from 65.5% to 44.0%. Similarly, for prasugrel, the prevalence was also observed to have decreased from 20.9% to 10.5%. However, we observed that the prevalence of prescriptions for ticagrelor increased from 13.7% to 45.6%. Interestingly, in the year 2018, the market share of ticagrelor appears to be exceeding the clopidogrel share (45.6% vs 44.0%). For the MDCR sample, we observed similar patterns. Although decreasing with years, the prevalence of clopidogrel was higher compared to CCAE for the entire period of study. The prevalence changed from 79.4% to 66.2% in the MDCR sample for clopidogrel prescription. The adoption of prasugrel also decreased with time from 9.9% to 5.6% from the year 2013 to 2018, so was also utilized less compared to the CCAE sample. However, the prevalence of ticagrelor prescription, although less compared to the CCAE sample, was found to be increasing from the years 2013 to 2018 (10.8% vs 28.2%).

(1.3) Difference in the prescription of P2Y12 inhibitors as per the technique of revascularization in the CCAE and MDCR populations:

We also looked at the difference in the annual prevalence of P2Y12 inhibitors based on the revascularization procedure from the year 2013-2018. For the CCAE data (**Appendix Table 3.4**), after PCI the prevalence of clopidogrel prescription decreased from 62.2% to 40.0% from the year 2013 to 2018. At the same time, prasugrel prevalence also decreased from 22.88% to 11.19%. However, an increasing pattern was

observed in the ticagrelor prescription as it increased from 14.92% to 48.81%. It is interesting to note that in 2018, the prevalence of prescription of ticagrelor was higher than clopidogrel (40.0% vs 48.8%). Yet, for other revascularization techniques i.e., CABG and Fibrinolysis, clopidogrel dominated the prescription fill for secondary CHD prophylaxis. For CABG, the prevalence of clopidogrel changed from 94.3% to 88.5% from the years 2013 to 2018. Similarly, for the MDCR sample (**Appendix Table 3.5**), the prescription share was dominated by clopidogrel, substantially. In the PCI group, although decreasing, the prescription share of clopidogrel varied from 77.8% to 64.6%; whereas, for prasugrel, it changed from 10.7% to 6.0%. For the ticagrelor arm, the prescription prevalence changed from 11.6% to 29.5%. For other revascularization procedures, clopidogrel was found to be the dominant prescription compared to the newer drugs as the prescription share of clopidogrel changed from 90.9% to 82.3% after CABG.

(1.4) Difference in the prescription of P2Y12 inhibitors among the patients with high bleeding risk and history of stroke or transient ischemic events:

We further looked at if there was a difference between the prescription fill of P2Y12 inhibitors as per patient characteristics. We first observed the prevalence of prescription among patients with bleeding risk (**Appendix Table 3.6**) as per the criteria defined by AHA (i.e., history of major bleeding, diabetes, anemia, chronic kidney disease, low body weight, and concomitant use of oral anticoagulants, steroids, or NSAIDs). We identified 38,146 patients in the CCAE sample and 23,328 patients in MDCR data with at least one bleeding risk factor as per AHA. For the CCAE study sample, the prevalence of clopidogrel prescription reduced from 70.6% to 50.6%, and a similar pattern of reduction

of prevalence was observed in prasugrel prescription as well. For ticagrelor, for the study period, the prevalence increased from 12.0% to 40.1%. It is interesting to note that for the commercial claim study sample, the use of ticagrelor increased substantially with time irrespective of bleeding risk. We also observed a similar pattern in the MDCR study sample although clopidogrel was the most prevalent prescribed drug. For clopidogrel, during the study period, clopidogrel prevalence reduced from 82.18% to 71.09% from the year 2013 to 2018. For prasugrel, the prescription share reduced from 8.23% to 5.38%; whereas the ticagrelor share continued to increase from 9.59% to 23.54%. We also looked at the prescription patterns of P2Y12 inhibitors among patients with a history of stroke (**Appendix Table 3.7**). We identified 2721 and 2600 patients with a history of stroke in the past six months in CCAE and MDCR study samples. For CCAE, we observed 77.84%, 7.61%, & 14.55% prescription share corresponding to clopidogrel, prasugrel, & ticagrelor. And for the MDCR sample, we found that the prescription share for clopidogrel, prasugrel, & ticagrelor was 84.88%, 5.19%, & 9.92%, respectively.

(1.5) Trend of P2Y12 inhibitors in CCAE and MDCR:

To determine the difference in the 'prescribing trend' over time, we looked at the proportion of patients prescribed with different P2Y12 inhibitors in every quarter (3 months) from the year 2013 to 2018. For CCAE data **(Appendix Figure 3.1)**, we observed that the prescription of ticagrelor surpassed the market share of clopidogrel in the year of 2018 between quarter first and second. However, for the MDCR sample, although the market share of ticagrelor appears to be on an increasing trend, it remained well below the clopidogrel share for secondary CHD prophylaxis as shown in **Appendix Figure 3.2**. We also looked at the trends of P2Y12 inhibitors prescribing statistically if it

was changing over time. We found that there was a significant difference at p=0.05 in the trend of each P2Y12 inhibitor fill with time for both of the data samples (**Appendix Tables 3.8 & 3.9**). It is interesting to note that in both of the samples, the prasugrel share was decreasing with time.

(B) PREDICTORS OF P2Y12 INHIBITORS UTILIZATION IN CCAE AND MDCR POPULATIONS:

We observed the predictors of drug selection in both of the data samples (**Tables 3.1 & 3.2**) using Andersen's behavior model for drug selection controlling for predisposing, enabling, and need variables using multivariate logistic regression. With these adjusted comparisons, we explored if statistical significance was persisted for the variables in exploratory analysis in **Appendix Table 3.2**. Additionally, we explored which categories in the categorical variables were statistically different and responsible for the significant difference at p=0.05 in the unadjusted comparisons.

a. Predisposing demographic variables

(i) Age of the patients: For predisposing demographic variables in the CCAE sample (**Table 3.1**), for the age variables, '56-65 years' age group was associated with 10.5% higher odds of clopidogrel use over ticagrelor compared to '18-45 years' age group which was statistically significant (OR 1.11 (1.02-1.20)). Similarly, for this age group, clopidogrel use was associated with 16% higher odds compared to prasugrel (OR 1.16 (1.05-1.273)). However, we didn't find any difference among the patients with 46-55 years age bracket compared to the 18-45 years old group. On the other hand, for the MDCR group (**Table 3.2**), compared to patients in the 65-74 years age bracket, patients aged 85 years and above were associated with higher odds of filling clopidogrel

compared to ticagrelor (OR 2.36 (2.012-2.77)). Similarly, clopidogrel was associated with higher odds of being filled compared to prasugrel as the odds of filling clopidogrel was 8.9 times the odds of prasugrel fill (OR 8.94 (6.03-13.25)). Ticagrelor was more likely to be filled compared to prasugrel (OR 3.87 (2.53-5.94)) when these two groups were compared. While comparing patients in the 75-84 age bracket with 65-74-year-old patients, we observed that patients who were 75-84 years aged had 41% higher odds of clopidogrel fill compared to ticagrelor (OR 1.41 (1.28-1.56)), and were associated with 3.2 times higher odds of clopidogrel compared to the odds of prasugrel use (OR 3.2 (2.717-3.773)). Additionally, the odds of ticagrelor use were 2.3 times the odds of prasugrel use (OR 2.33 (1.93-2.80)). It appeared that increasing age was associated with greater use of clopidogrel for both of the sample populations compared to newer P2Y12 inhibitors.

(ii) Gender of the patients: Male population in the CCAE sample was associated with 9% and 21% lower odds of clopidogrel use compared to ticagrelor (OR 0.91 (0.86-0.97)) and prasugrel (OR 0.788 (0.73-0.85)), respectively. However, ticagrelor was preferred over prasugrel as it was associated with 14% higher odds of being filled compared to ticagrelor (OR 0.86 (0.79-0.94)). On the other hand, for the MDCR sample, we didn't find any difference in the prescription fill of clopidogrel and ticagrelor; nevertheless, the male population was less likely to fill clopidogrel as compared to prasugrel (OR 0.77 (0.66-0.90)) and ticagrelor compared to prasugrel (OR 0.78 (0.66-0.93)). Based on these results, it appears that the female population filled newer P2Y12 inhibitors more often compared to their male counterparts.

(iii) Region to which patients belong: We also observed that for the CCAE sample, Northeast, Northcentral, and West regions were more likely to fill clopidogrel compared to the South region over prasugrel as these regions were associated with 46%, 59%, and 44% higher odds of clopidogrel prescription over prasugrel i.e. (OR 1.46 (1.33-1.59)), (OR 1.59 (1.47-1.73)), and (OR 1.44 (1.31-1.58)), respectively. Additionally, compared to the South region, the West and Northeast region were associated with 56% and 11% higher odds of clopidogrel prescription over ticagrelor (OR 1.56 (1.44-1.69)) and (OR 1.11 (1.04-1.18)), respectively. As far as the MDCR sample was concerned, compared to the South region, Northcentral and West regions were more likely to have filled clopidogrel compared to ticagrelor i.e. (OR 1.22 (1.09-1.36)) and (OR 1.36 (1.15-1.59)), respectively. Similarly, compared to the South region, Northeast, Northcentral, and West regions were more inclined towards clopidogrel fill over prasugrel i.e. (OR 1.45 (1.18-1.76); $p<0.01$), (OR 1.55 (1.31-1.84)), and (OR 1.31 (1.05-1.65)), respectively. We also observed that Northeast and Northcentral regions were more likely to fill ticagrelor over prasugrel compared to the South region i.e. (OR 1.28 (1.03- 1.60)) and (OR 1.38 (1.14-1.67)), respectively.

b. Enabling variables:

(i) Insurance plan type: For enabling variables, we observed that in the CCAE sample, comprehensive plans were associated with 90% higher odds of clopidogrel prescription over ticagrelor (OR 1.90 (1.66-2.17)) and 13% lower odds of clopidogrel prescription compared to prasugrel (OR 0.83 (0.72-0.95)). However, in the MDCR sample, patients with HMO plans compared to PPO pans were more likely to fill clopidogrel compared to ticagrelor (OR 1.30 (1.12-1.52)). For other comparisons between the plans, we didn't

find any statistically significant differences (at p=0.05) between one drug use over the other.

(ii) Index year of P2Y12 inhibitor prescription: Over time, the use of clopidogrel decreased annually compared to ticagrelor in the CCAE sample. For example, compared to the year 2013, from the year 2014 to 2018, clopidogrel was associated with statistically significant 37% to 85% lower odds of being prescribed compared to ticagrelor i.e. (OR 0.63 (0.57-0.70)) and (OR 0.15 (0.14-0.17)), respectively. Similarly, ticagrelor was highly likely to be filled over prasugrel as the odds of use ticagrelor was 1.6 to 7.8 times the odds of prasugrel use from the year 2014 to 2018 compared to the year 2013 (OR 1.60 (1.42-1.81)) and (OR 7.77 (6.78-8.91)), respectively. Additionally, for the year 2015 and 2018, the odds of clopidogrel prescribing were found to be significantly higher compared to prasugrel use (OR 1.14 (1.03-1.27)) and (OR 1.16 (1.03-1.32)), respectively. We observed similar patterns in the MDCR sample. We saw a significant drop of clopidogrel fill compared to ticagrelor fill with time as the odds of clopidogrel use reduction compared to ticagrelor reduced from 22% to 78% for the year 2014 to 2018 compared to 2013. Similarly, we observed a significant increase in the odds of ticagrelor use over the odds of prasugrel use increasing from 2.9 times to 10 times over the years (2014-2018 vs 2013).

c. Need variables

(i) Type of revascularization: Looking at the possible need variables, in the CCAE sample, for the secondary CHD prophylaxis after revascularization, those undergoing CABG compared to PCI were more likely to be prescribed with clopidogrel as the odds of prescribing clopidogrel were 1.73 times the odds of prescribing ticagrelor (OR 1.73

(1.38-2.153)). Similarly, the odds of prasugrel were lower compared to clopidogrel for those undergoing CABG compared to PCI (OR 0.67 (0.50-0.89)). We observed similar patterns in MDCR data i.e. clopidogrel vs ticagrelor (OR 1.30 (1.03-1.65)) and clopidogrel vs prasugrel (OR 1.53 (1.04-2.24)); however, there was no difference between the prescription fill of ticagrelor and prasugrel.

(ii) Type of stent: We continued by looking at the adjusted difference of P2Y12 inhibitor use between the patients undergoing revascularization with DES compared to BMS. In the CCAE sample, among those undergoing PCI with stent implantation, the odds of clopidogrel were 14% lower compared to ticagrelor when patients were revascularized using DES over BMS (OR 0.86 (0.80-0.92)). Similarly, clopidogrel was also associated with lower odds of use compared to prasugrel if patients were revascularized using DES over BMS (OR 0.86 (0.78-0.94)). For the MDCR sample, we witnessed a greater likelihood of newer P2Y12 inhibitors use over clopidogrel if DES were used compared to BMS for revascularization e.g., clopidogrel vs ticagrelor (OR 0.81 (0.71-0.92)) and clopidogrel vs prasugrel (OR 0.67 (0.54-0.83)). Thus, newer medications were preferred over clopidogrel for both of the populations.

(iii) Type of ACS presentation: For the ACS presentation in the CCAE sample, among patients with STEMI compared to NSTEMI/UA, the odds of prescribing clopidogrel were lower in comparison of ticagrelor and prasugrel prescribing (OR 0.72 (0.686-0.759)) and (OR 0.76 (0.72-0.81)), respectively. We observed a similar pattern in the MDCR population as well i.e., clopidogrel vs ticagrelor (OR 0.65 (0.71-0.92)) and clopidogrel vs prasugrel (OR 0.74 (0.64-0.85)). Additionally, we observed that ticagrelor was

associated with 24% increased odds of being filled compared to prasugrel (OR 1.24 (1.05-1.45)).

(iv) Comorbidities in the past 6 months: As far as the Elixhauser index was concerned, we observed that a higher category of the Elixhauser index was associated with increased odds of clopidogrel use over ticagrelor for both of the study samples.

(v) High bleeding risk: We continued to see a difference in the prescription fill of different P2Y12 agents among the patients at an increased risk of bleeding defined as per AHA guidelines as (i) high-risk comorbidities in the past six months i.e. diabetes mellitus, anemia, chronic kidney disease (CKD), and low body weight (LBW) (ii) history of prior major bleeding (i.e. intracranial (IC), gastrointestinal (GI) and any other major bleeding)), and (iii) the concomitant use of oral anticoagulants, Rx NSAIDs, or steroids. For the CCAE sample, having a diabetes diagnosis in the past 6 months was associated with 10% lower odds of ticagrelor prescribing compared to prasugrel. Patients with chronic kidney disease were more likely to be prescribed clopidogrel over ticagrelor and prasugrel i.e. (OR 1.20(1.04-1.1.37)) and (OR 1.23 (1.04-1.46)), respectively. Having low body weight was also associated with the increased use of clopidogrel compared with ticagrelor and prasugrel (OR 1.68 (1.09-2.55)) and (OR 1.87 (1.03-3.39)), respectively. For patients with a history of prior bleeding within the last 6 months, the use of clopidogrel was associated with 19% and 28% higher odds of clopidogrel compared to ticagrelor (OR 1.19 (1.05-1.34)) and prasugrel (OR 1.28 (1.10-1.49)). We also looked at the P2Y12 inhibitors use concomitantly with high-risk medications as a risk of high bleeding risk. We observed that clopidogrel was associated with 52% and 77% higher odds compared to ticagrelor (OR 1.52 (1.39-1.66)) and prasugrel (OR 1.77 (1.57-2.00)).

Additionally, we observed 23% higher odds of ticagrelor prescription over prasugrel (OR 1.23 (1.07-1.41)). However, in the Medicare sample, having diabetes and CKD as a high bleeding risk did not reflect any differences in the prescription fill of P2Y12 inhibitors. Yet, patients with low body weight were associated with increased odds of clopidogrel fill compared to ticagrelor i.e. (OR 1.92 (1.12-3.26)). Additionally, anemia diagnosis in the past 6 months was associated with lower odds of clopidogrel use over ticagrelor (OR 0.79 (0.65-0.97)). And among those who had experienced a major bleeding event in the past were associated with 41% higher odds of clopidogrel fill over ticagrelor (OR 1.41 (1.18-1.67)). Moreover, compared to prasugrel, ticagrelor was associated with 26% lower odds of prescription fill (OR 0.74 (0.55-1.00)) among patients with a history of major bleeding. Additionally, we observed that clopidogrel was associated with a higher odd of being filled compared to ticagrelor (OR 1.8 (1.56-2.08)) and prasugrel (OR 1.60 (1.28-1.98)) if it was filled concomitantly with high bleeding risk medications (i.e., oral anticoagulants, Rx NSAIDs, or oral corticosteroids).

(vi) History of medications in the past 6 months: We further looked for any differences in the prescribing of P2Y12 inhibitors given the six-month history of medication uses which may affect the cardiovascular system. In the CCAE sample, prior antiplatelet drug use was associated with 19% lower odds of clopidogrel use compared to prasugrel (OR 0.81 (0.71-0.93)). For those patients who were the ace inhibitors users, clopidogrel use was associated with 10% higher odds than ticagrelor (OR 1.11 (1.04-1.19)). Among beta-blockers users, the use of clopidogrel was associated with 23% and 11% higher odds compared to ticagrelor and prasugrel (OR 1.23 (1.15-1.31)) and (OR 1.11 (1.03-1.21)), respectively. Ticagrelor use was associated with lower odds of being prescribed compared to prasugrel among beta-blocker users (OR 0.90 (0.83-0.99)).

Patients with a history of antiarrhythmics use were more likely to be prescribed clopidogrel compared to ticagrelor as clopidogrel use was associated with 78% higher odds (OR 1.78 (1.23-2.58)). Similarly, among the users of cardiac glycosides, the odds of clopidogrel use were 2.3 times the odds of ticagrelor use (OR 2.26 (1.31-3.91)). Among diabetics with SGLT inhibitors history, clopidogrel use was associated with 20% lower odds of use compared to ticagrelor (OR 0.80 (0.66-0.96)). The use of anti-lipid drugs in the past was also associated with lower odds of clopidogrel prescription over prasugrel (OR 0.88 (0.82-0.95)). For those prescribed with PPIs in the past, clopidogrel use was associated with 11% lower odds of use compared to prasugrel (OR 0.89 (0.82-0.97)). We then looked at the MDCR group if the drug use in the past was associated with any difference in the prescribing of P2Y12 inhibitors. We observed that antiplatelet drug use in the past was associated with lower odds of clopidogrel use compared to ticagrelor (OR 0.78 (0.67-0.91)) as seen in unadjusted comparisons. For antihypertensives, those who were users of alpha-beta and beta-blockers were associated with higher odds of clopidogrel fill compared to ticagrelor (OR 2.59 (1.32-5.12)) and (OR 1.17 (1.05-1.29)), respectively. Additionally, loop diuretics use in the past was also associated with higher odds of clopidogrel use over ticagrelor (OR 1.21 (1.04-1.40)). Interestingly, antidepressant use in the past was also associated with higher odds of clopidogrel fill compared to ticagrelor (OR 1.19 (1.05-1.35)).

CHAPTER 4: STUDY 2

Comparative Effectiveness of P2Y12 Inhibitors for Secondary Prophylaxis in Acute Coronary Syndrome after Percutaneous Coronary Intervention

4.1. Introduction

Acute coronary syndrome (ACS) is characterized by coronary artery occlusion resulting in reversible or irreversible myocardium injury, morbidity, and mortality.[10,11] The complications in ACS present as (1) ST wave elevated myocardial infarction (STEMI), in which complete occlusion of a coronary artery for 2-4 hours takes place affecting the full thickness of the myocardium[12] and (2) Non-ST wave elevated acute coronary syndrome (NSTE-ACS), which is further subdivided into (a) NSTEMI, with elevated biomarkers, and (b) unstable angina (UA), those without elevated biomarkers.[9] In NSTEMI, deprivation of oxygen also occurs but does not result in full-thickness necrosis.[12,13] In ACS, there is an emergent need for restoration of blood supply to ischemic myocardium to limit ongoing damage and improve short and long-term outcomes.[182] Revascularization using percutaneous coronary intervention (PCI) in patients presenting with ACS is a common practice. The goal of PCI is to open up the occluded coronary artery and restore blood flow to reduce the amount of heart muscle necrosis following ACS.[183] Unfortunately, following PCI there is substantial risk of rehospitalization within 30 days due to recurrent ACS events.[184-188] Approximately 60% of the cost to manage ACS is consumed on recurrent ACS events.[87]

Recurrent ACS prophylaxis is essential to reduce mortality and adverse cardiovascular outcomes of ACS survivors post revascularization with PCI and is

strongly recommended by the American Heart Association and the American College of Cardiology (AHA/ACC).[60] Following initial revascularization, long-term management to prevent recurrence of ACS involves the use of dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor (i.e. clopidogrel, prasugrel, or ticagrelor).[15] Although effective, clopidogrel-based DAPT is hampered by its slow onset of action,[20] variable inter-individual response,[21] and treatment resistance,[22-24] resulting in a high risk of treatment failure. Newer P2Y12 inhibitors including prasugrel and ticagrelor have shown better pharmacokinetic profiles and efficacy compared to clopidogrel.[25-29] Additionally, in head-to-head randomized controlled trials (RCTs) comparing newer P2Y12 inhibitors with clopidogrel, prasugrel and ticagrelor have shown better efficacy in terms of reduction of stent thrombosis, ischemic events, recurrent MI, and stroke compared to clopidogrel in ACS.[25,26] Given better pharmacokinetics and greater efficacy in RCTs, the use of newer P2Y12 inhibitors (i.e. prasugrel and ticagrelor) is suggested, if not contraindicated.[62] [25] This has resulted in an increased utilization of these agents in clinical practice.[63]

However, the effectiveness of prasugrel and ticagrelor compared to clopidogrel in real-world ACS patients is not well studied, and it is unclear whether the RCT results replicate in standard clinical practice. PCI patients enrolled in the RCTs may not be representative of the general population (e.g., patients enrolled in RCTs tend to be healthier).[189,190] Also, RCTs often have limited sample size and are thus underpowered to evaluate differences in outcomes by key subgroups (e.g., age, sex, high bleeding risk, and comorbidities). Additionally, to our knowledge, prasugrel and ticagrelor have never been compared head-to-head in the US. Given these limitations, a 2020 FDA statement supports the increasing role of real-world evidence in healthcare decisions.[191]

Furthermore, no studies have compared newer antiplatelet drugs to clopidogrel for STEMI and NSTEMI/UA patients separately in real-world practice post PCI. The effect of these drugs may vary based on these clinical characteristics. For example, NSTEMI/UA patients tend to be older, having higher comorbidities, and lower short term and higher long term mortality compared to STEMI patients.[45,192] As such, antiplatelet drugs response may vary by ACS presentation. Also, female sex has been shown to predict poor prognosis, worse clinical outcomes, and higher complications and mortality rates following an MI compared to males in ischemic heart disease.[47, 48] It is unknown whether there are sex interactions of the effectiveness of DAPT therapies on outcomes following an ACS. Furthermore, current literature also lacks the information if newer P2Y12 inhibitors compared to clopidogrel are associated with better clinical outcomes based on the inserted stent whether bare-metal stents (BMS) or drug-eluting stents (DES). The main objective of this study is to evaluate the comparative effectiveness across P2Y12 inhibitors in a US real-world population overall and among key clinical subgroups.

4.2. Methods

Data Source

This analysis was conducted using the IBM MarketScan® databases from January 1, 2013, to December 31st, 2018. This database includes a large population of more than 30-50 million commercially insured beneficiaries in the Commercial Claims and Encounters (CCAE) and 1 million Medicare beneficiaries with supplemental benefits in the Medicare Supplemental and Coordination of Benefits (MDCR) data set every year across the United States. The CCAE sample comprised patients aged 18 to 65 years. The MDCR sample included patients aged ≥ 65 years. These data contain de-identified person-level information on enrollment, linked to inpatient, outpatient, and prescription claims. CCAE data contains information on healthcare coverage and service use of individuals under a variety of different insurance offerings including fee-for-service (FFS), capitated, preferred provider organization (PPO), health maintenance organization (HMO), and others. Whereas the MDCR database contains information on Medicare-eligible employees who have additional coverage through supplemental plans or employers. Similar to the CCAE files, the MDCR database also contains information on healthcare coverage and service use of individuals under a variety of plan offerings.

Study Design

We utilized a retrospective matched cohort study design to examine whether newer P2Y12 inhibitors (i.e., ticagrelor and prasugrel) are associated with better cardiovascular outcomes compared to clopidogrel following a PCI. The index date is defined as the date of P2Y12 inhibitor initiation within 14 days following a PCI. Prior

P2Y12 inhibitor users in the baseline period (6 months) were excluded to ensure incident drug use.

The initial cohort included patients aged ≥18 years discharged from the hospital or outpatient setting with a primary diagnosis of ACS. We included ACS patients if they were revascularized using a PCI. To identify ACS, we used validated International Classification of Disease 9 & 10 Clinical Modification codes (ICD-9 & 10-CM).[141-143] PCI procedures were coded using Current Diagnosis Procedure (CPT) codes, Healthcare Common Procedure Coding System (HCPCS), and ICD 9 and 10 procedure codes published previously.[69,161-164] The complete list of codes is given in **(Appendix Table 4.1).** The sample was limited to patients ≥18 years of age given that ACS is uncommon in younger patients.[193] We combined CCAE and MDCR data files in this study and also conducted a sensitivity analysis in which we studied the CCAE and MDCR sample populations separately given to examine the effect of age on effectiveness.

We included patients with continuous enrollment for at least 6 months in a health plan with medical and pharmacy benefits before the PCI procedure. Patients were also required to have continuous enrollment for these benefits until the day of follow-up (i.e. 30 days and 180 days) after the index P2Y12 inhibitor initiation to measure effectiveness. We used an intention to treat (ITT) approach[156] whereby we classified participants according to the first prescription of a P2Y12 inhibitor, and they remained in that category throughout the entire study period.

Three cohorts were constructed to compare the effectiveness of (1) ticagrelor versus clopidogrel, (2) prasugrel versus clopidogrel, and (3) ticagrelor versus prasugrel.

Schematic descriptions of the study design and patient inclusion are depicted in **Figure 4.1** and **Appendix Figure 4.1**, respectively.

Outcome Variables

The primary effectiveness outcome was hospitalization due to a composite cardiovascular outcome including recurrent myocardial infarction, unstable angina, recurrent revascularization (Fibrinolysis, PCI, or coronary artery bypass graft (CABG)), stroke (ischemic or hemorrhagic), and heart failure at day 30 and 180 after the start of the index P2Y12 inhibitor. The secondary effectiveness outcomes were the individual events of stroke (ischemic or hemorrhagic), coronary artery disease (CAD) events (including recurrent myocardial infarction, unstable angina, or recurrent revascularizations), and peripheral artery disease (PAD) occurring at days 30 and 180 after the index P2Y12 inhibitor initiation. The complete list of validated ICD codes for outcomes of interest is given in **Appendix Table 4.1.**

Confounding Variables

Potential confounding variables were identified in the 6 months (or more) prior to the initial PCI procedure. We grouped the confounding variables based on Andersen's Behavioral Model (ABM) for Health Services Utilization.[134] The ABM model incorporates both individual and contextual determinants of health care use. Control variables in the ABM model included:

(1) Predisposing variables included age, sex, and geographical region.

(2) Enabling characteristics that may facilitate the delivery of healthcare services were comprised of insurance plan/coverage variables. These included exclusive

provider organization (EPO), health maintenance organization (HMO), point-of-service (POS), preferred provider organization (PPO), consumer-driven health plan (CDHP), and high-deductible health plans (HDHP).

(3) Need variables represented both perceived and actual health condition mandates that may increase or decrease the need for treatment or the type of treatment provided (e.g., which P2Y12 inhibitor was selected). This included the Elixhauser comorbidity index (EI) [114], high bleeding risk, and medication history. High bleeding risk was defined according to AHA guidelines[165] as (i) high-risk comorbidities in the past six months (i.e. diabetes mellitus, anemia, chronic kidney disease (CKD), and low body weight (LBW)) (ii) history of prior major bleeding (i.e., intracranial (IC), gastrointestinal (GI) and any other major bleeding)), and (iii) concomitant use of high-risk medications (i.e., oral anticoagulants, Rx non-steroidal anti-inflammatory drugs (NSAIDs), or steroids). We defined concomitant use of drugs if any of these high-risk medications were filled (i) within 15 days before or (ii) within 30 days after the index dispensing day of a P2Y12 inhibitor. Patients were also required to have at least 30 days' supply of these high-risk medications to ensure concomitant use (overlap).

To identify comorbidities in the past 6 months, we used validated international classification of disease 9 & 10 clinical modification codes (ICD-9 & 10-CM). [141-143] The complete list of ICD, HCPCs, and CPT codes used is given in **Appendix Table 4.1**. All the drug claims in this study were identified by National Drug Code (NDC) from outpatient pharmacy claims data using the prescription fill date.

Statistical Analysis

Descriptive statistics, including counts and percentages, were presented for all of the pairwise comparisons**.** To control for confounding, a propensity score (PS) for each patient was estimated using multivariate logistic regression. This model incorporated potential treatment and outcomes predictors as independent variables (discussed in the "confounding variables" section above) and group status (e.g., clopidogrel initiators vs prasugrel initiators) as an outcome. We matched patients 1:1 on their PS using the nearest-neighbor matching technique without replacement within a caliper of 0.05[150] of the standard deviation of the logit of the propensity score for each pair (i.e. 'ticagrelor versus clopidogrel', 'prasugrel versus clopidogrel', and 'ticagrelor versus prasugrel').

As this study included data from 2013 to 2018, we utilized exact matching to control for the year of treatment initiation, the addition of new agents over time, and changes in the adoption of these treatments. Using calendar time-specific PS matching is believed to better control for confounding under these conditions.[194] To assess the balance of patient confounders at baseline, standardized differences were evaluated in all of the PS matched comparisons. An absolute standardized difference of ≤0.1 indicates a negligible difference in potential confounders and balanced matched cohorts.[195]

We utilized Cox-proportional hazards regression models to perform time to event analysis to compare effectiveness outcomes across different antiplatelet drugs over the 30- and 180-day follow-up time intervals. Patients were followed until the outcome of interest was observed or administrative censoring due to reaching the follow-up time-

frame of interest (30 or 180 days) or the end of the period for which data was available (December 31, 2018).

The results were presented as hazard ratios (HRs) with their 95% confidence intervals (CIs). The proportionality hazard assumption was tested by including an interaction term between exposure and time of follow-up in the Cox-proportional hazards models. If there was any violation, we planned to run stratified models for those time-varying exposure levels. Finally, we presented the cumulative incidence, person-days, and absolute risk differences (in percentage) and number needed to treat (NNT) to prevent one additional outcome for all the PS matched pairwise comparisons.

We also ran Cox-proportional hazards regression models before matching the patients on their PS to see the difference in the outcomes in unadjusted comparisons. We didn't include any covariates in these unadjusted models.

Subgroup Analyses

We analyzed the overall ACS population in the primary analysis and performed several subgroup analyses to look at differences in comparative effectiveness in groups with varying risk (i.e., ACS presentation (STEMI and NSTEMI/UA), type of stent (DES, and BMS) and sex. STEMI and NSTEMI patients were identified using validated and published ICD 9 and 10 codes **(Appendix Table 4.1)**.[133,141-143,196]

4.3. Results

Population Characteristics

We identified 90,529 ACS patients with continuous enrollment in the 6 months prior to their initial PCI. For the future outcomes, after we applied 30 days and 180 days future continuous enrollment criteria, we had 79,145 and 62,230 patients in the dataset for 30 days and 180 days outcomes, respectively. Before PS matching, for the 30-day outcomes **(Appendix Table 4.2)**, we identified 42,720 patients who initiated clopidogrel, 24,414 who initiated ticagrelor, and 12,011 prasugrel within 14 days after the index PCI, respectively. Similarly, for 180-day outcomes, we observed 33,898, 18,588, and 9,744 patients on clopidogrel, ticagrelor, and prasugrel, respectively. The comparisons of the patients on different P2Y12 inhibitors in the overall population and sensitivity analysis (CCAE and MDCR samples) before PS matching are given in **Appendix Tables 4.2-4.4.**

After PS matching, for the 30-day outcome cohort **(Appendix Table 4.5)**, we had 21,549 (clopidogrel versus ticagrelor), 11,776 (clopidogrel versus prasugrel), and 11,263 (ticagrelor versus prasugrel) matched pairs to compare outcome events in pairwise comparisons. For the clopidogrel vs ticagrelor matched pairs, the majority of the patients came from the 45-64 years age bracket, were predominantly males, and a higher number of patients had an Elixhauser Index of 0 for the associated comorbidities. Importantly, a substantial number of patients were at increased bleeding risk. Very similar characteristics for the other matched pairs (i.e. clopidogrel versus prasugrel and ticagrelor versus prasugrel) were observed at 30 days **(Appendix Table 4.5)**. A detailed description of all the PS matched comparisons including sensitivity analysis (CCAE and MDCR samples individually) is given in **Appendix Tables 4.5-4.10**. For all the pairwise

comparisons in this study, the standardized differences were less than 10% indicating well-balanced cohorts for the effectiveness outcomes comparisons.

Comparative Effectiveness

Before PS matching, at 30 days we observed 1,172 (2.74%) patients with composite cardiovascular outcomes in the clopidogrel group, 598 (2.45%) in the ticagrelor group, and 247 (2.06%) in the prasugrel group, respectively (**Table 4.1)**. Also, in 180 days, we observed a substantial increase in the number of composite outcomes in each group i.e., clopidogrel (2431 (7.17%)), ticagrelor (1059 (5.70%)), and prasugrel (498 (5.11%)). It should be noted that the composite outcome was derived mainly by coronary artery disease events in all of these groups.

The HRs and their 95% CIs are given in **Table 4.2** and **Tables 4.3 & 4.4** (sensitivity analysis) for all the Cox-regression models for primary effectiveness outcomes at different time intervals. Also, the number of events after PS matching is given in **Table 4.5** (primary effectiveness) and **Appendix Table 4.12** (secondary effectiveness)**.**

Risk of Composite Cardiovascular Outcome:

1. **Ticagrelor vs clopidogrel users:** Before PS matching **(Table 4.2)**, ticagrelor was associated with an 11% reduced risk of the composite cardiovascular outcome (HR (95%CI): 0.89 (0.81-0.99)) compared to clopidogrel at 30 days. However, this effect was not significant after PS matching (HR (95%CI): 0.98 (0.87-1.11)). Similarly, at 180 days, we observed a 21% risk reduction associated with ticagrelor that not significantly different compared to clopidogrel

in PS matched comparisons. For the absolute risk differences, after PS matching, ticagrelor was associated with 0.04% and 0.07% lower risk of composite cardiovascular compared to clopidogrel at 30 and 180-day follow-up **(Table 4.5)**. Also, approximately 2,394 patients on the 30th day (NNT=2394) and 1,406 patients on the 180th day (NNT=1,406) were needed to treat with ticagrelor to prevent one composite cardiovascular outcome compared to clopidogrel **(Table 4.5)**.

In subgroup analyses **(Table 4.2)**, we did not see any differences between the groups by type of ACS i.e., STEMI or NSTEMI and stent types i.e., DES or BMS. However, at 30 days follow up, ticagrelor was associated with a 20% lower risk compared to clopidogrel in the female population (HR (95%CI): 0.80 (0.65-0.98)) which was not different at 180 days (HR (95%CI): 0.91 (0.78-1.07)). For both follow-up times, there were no differences in both drugs in the male population.

2. **Prasugrel vs Clopidogrel users:** Before matching, at 30 days **(Table 4.2)**, compared to clopidogrel, prasugrel was associated with a 25% reduced risk of composite cardiovascular outcome (HR (95%CI): 0.75 (0.65-0.86)) that was not significantly different in PS matched comparison (HR (95%CI): 0.99 (0.83-1.18)). Similarly, at 180 days, we observed a 29% reduced risk associated with prasugrel (HR (95%CI): 0.71 (0.64-0.78)) which was not significantly different after PS matching (HR (95%CI): 0.96 (0.85-1.08)).

   In PS matched comparison, the absolute risk difference was in favor of prasugrel i.e., 0.02% (at 30th day; NNT=5,887) and 0.22% (at 180th day;

NNT=457) compared to clopidogrel **(Table 4.5)**. Subgroups showed similar results to the primary analysis.

3. **Prasugrel vs ticagrelor users:** In the unmatched analysis prasugrel, compared to ticagrelor (before matching) was associated with a statistically significant 16% and 11% reduced risk **(Table 4.2)** of the composite cardiovascular outcome at 30 days (HR (95%CI): 0.84 (0.72-0.97)) and 180 days (HR (95%CI): 0.89 (0.80-0.99)), respectively. However, there was no difference between the groups in PS matched comparisons **(Table 4.2)** and for 30th and 180th day, respectively. Nevertheless, prasugrel was associated with an absolute risk difference of 0.28% and 0.26% compared to ticagrelor at the 30th (NNT=351) and 180th day (NNT=380) of follow-up. The results for time to event analysis were similar in the subgroup analyses.

Sensitivity Analysis: We observed similar results in the sensitivity analysis where we examined associations separately in the CCAE and MDRC samples **(Table 4.3 & 4.4)** for the primary analysis. However, in the subgroup analysis in the CCAE sample **(Table 4.3)**, we observed a 33% lower risk associated with prasugrel compared to clopidogrel in the female population in 30 days (HR (95%CI): 0.67 (0.48-0.94)). Additionally, ticagrelor was found to be associated with better outcomes compared to prasugrel in females as prasugrel was associated with 84% higher incidence of composite cardiovascular outcome (HR (95%CI): 1.84 (1.08-3.13)) at 180 days in the MDCR sample **(Table 4.4)**. Also, those who were managed with BMS stent in the CCAE sample **(Table 4.3)** and prescribed prasugrel were associated with a reduced risk of 43% at 180th day compared to ticagrelor.

For the secondary outcomes **(Appendix Table 4.11 & 4.12)** (i.e., individual events of stroke, cardiovascular events (acute MI, UA, and revascularizations), and heart failure, and PAD) we did not see any difference among the groups.

4.4. Discussion

In this real-world US-based study among patients undergoing PCI following ACS events, we observed that ticagrelor and prasugrel were associated with statistically significant reduced risk of composite cardiovascular outcomes, relative to clopidogrel, in crude comparisons at 30 and 180 days of follow-up. Nevertheless, in the primary analysis with PS matching, ticagrelor, prasugrel, and clopidogrel users were not different for primary (i.e., composite cardiovascular outcome) and secondary effectiveness endpoints in either follow-up period. However, in subgroup analysis ticagrelor was associated with a 20% lower risk of composite cardiovascular events in the female population compared to clopidogrel at 30 days, but not at 180 days. Also, no differences in effectiveness outcomes were visible between ticagrelor versus prasugrel users. In a sensitivity analysis, prasugrel was associated with a 33% lower risk of the 30-day composite cardiovascular outcome compared to clopidogrel in CCAE sample. Additionally, among patients managed with a BMS stent prasugrel was associated with a 43% lower risk compared to clopidogrel in 180-day outcomes in CCAE sample. Finally, in the MDCR population, ticagrelor was associated with a lower risk of composite cardiovascular events at 180 days compared to prasugrel in the female population.

Ticagrelor vs Clopidogrel: In our study, we observed no difference in composite cardiovascular outcomes associated with clopidogrel users compared to ticagrelor users. However, in the PLATO trial, ticagrelor was associated with better efficacy compared to clopidogrel in ACS, discordant with our finding. Differences between the PLATO trial findings and our results may stem from differences in the populations studied, with the majority of patients in the PLATO trial comprising non-US populations.

Importantly, the North American population was not found to benefit from ticagrelor compared to clopidogrel in a subgroup analysis of PLATO trial[26,124], which is consistent with our results. A possible reason behind this regional interaction in PLATO is hypothesized to be due to the higher use of high dose aspirin use during the maintenance phase in the US population compared to rest of the world. [124]

In addition, unlike our study which used ICD codes to identify ACS diagnosis, the PLATO trial confirmed the presence of ACS through EKG interpretation and a rise in cardiac specific enzymes which indicate the presence of tissue necrosis. It is important to note that in the PLATO trial, patients were managed with either BMS or the older first-generation DES stent. Over the years there has been significant advancement in the designs of DES which are already associated with lower stent thrombosis.[53,197] Our study includes data dating back to 2013, a full four years following publication of the PLATO trial results. Over this time, better designs of DES stents may also contribute to differences in the results of our study compared to PLATO.

Observational studies comparing ticagrelor and clopidogrel have yielded mixed results. Similar to our study, two recently conducted observational studies[64,65] also reported no difference between ticagrelor and clopidogrel in one year rates of major adverse cardiovascular events and net adverse clinical events. Nevertheless, ticagrelor was associated with better clinical outcomes at 24 months in a national registry of Sweden[66], and in a multicenter observational study studying these drugs for one year[198]. With the exception of a US-based study that examined outcomes using electronic health records, these studies were conducted outside of the US.[64] The US-based study did not compare prasugrel and clopidogrel, which we have reported in our study. These results

are important given that the ACS management may differ based on the practice patterns, healthcare system, and reimbursement policies between different countries. Thus, the results of studies from other country may not be applicable to the US population. For example, a population based study comparing the treatment and outcomes of US and Sweden population indicated better long term survival in US population. This study also reported higher use of PCI in US compared to Sweden.[199]

Prasugrel vs Clopidogrel: We found no differences in outcomes comparing clopidogrel and prasugrel for composite cardiovascular events. However, contrary to our results, prasugrel in TRITON–TIMI 38 RCT showed better efficacy in terms of reduction in ischemic events and stent thrombosis. The possible reason for this difference may be due to the variation in the study designs and the fact that in TRITON–TIMI 38 RCT, patients underwent a scheduled PCI, which was not possible to determine in our observational study. Nevertheless, like our study, another observational study comparing clopidogrel and prasugrel reported no difference between the drugs using data from a prospective PCI registry of 8 centers in the US.[30] We also observed similar effectiveness of clopidogrel and prasugrel in the elderly population (MDCR sample) consistent with a multicenter RCT.[200]

Prasugrel vs Ticagrelor: We found no difference in the outcomes between prasugrel and ticagrelor cohorts. However, an RCT[128] comparing these two drugs reported better effectiveness outcomes with prasugrel in a head-to-head comparison. In our study with patients managed with BMS, prasugrel was associated with significantly lower composite cardiovascular events than ticagrelor for 180 day outcomes. However, there was no effectiveness difference among those managed with

DES. This should be noted that DES stents are associated with better clinical outcomes compared to BMS.[53,197] Thus, the difference in effectiveness outcome might be due to the BMS stent and not due to the drugs because the effect was similar if the patients were managed with DES for this patient subgroup.

Sex: In females in our study, ticagrelor was associated with a 20% lower risk of composite cardiovascular outcome at 30 days compared to clopidogrel. Additionally, in sensitivity analysis examining 30 day outcomes in the CCAE population, prasugrel was associated with a 33% lower risk compared to clopidogrel in female subgroup. Sex-differences in pathophysiology have been reported to be responsible for variation in ischemic changes in the coronary arteries among females and males with ACS. Females tend to have coronary artery microvascular dysfunction and plaque erosion resulting in thrombus and MI. In males plaque rupture is thought to be principally responsible for an MI.[49,50] Given that poor prognosis is reported among females in IHD,[47] aggressive treatments with newer P2Y12 agents compared to clopidogrel might have been responsible for better outcomes in females in our study. Additionally, we found evidence that females in the MDCR sample had an 84% higher risk of composite cardiovascular events with prasugrel compared to ticagrelor.

Current AHA/ACC recommends secondary prevention after ACS for 12 months based on Cure trial reported in 2011.[41,201] Given that second-generation DES have become preferred in clinical practice and are believed to be associated with lower restenosis[53,197], prophylactic use of P2Y12 inhibitors for a shorter time i.e., six months or less may be desired to prevent bleeding events and is recommended by AHA/ACC guidelines. In our study, we report the most current evidence that is currently lacking in

the US population as we studied the difference between the effectiveness of ticagrelor and prasugrel compared to clopidogrel at shorter time intervals, i.e., 30 and 180 days. The results of our study are particularly of clinical interest given the higher 30 days hospital readmission rates following revascularization.[185-188] We found no difference in ACS readmission rates between clopidogrel, and newer P2Y12 inhibitors (prasugrel and ticagrelor) at 30 or 180 days in a large commercially insured real world population of US patients. As clopidogrel appears to be similar in effectiveness to newer agents and is less expensive, clopidogrel use may save a significant amount of cost attributed to the management of ACS post PCI.

Strengths and Limitations

This study has various strengths. We conducted head-to-head comparisons of all the P2Y12 inhibitors used for secondary ACS prophylaxis. The sample size was large which enabled us to conduct analyses in various subgroups. For example, we evaluated STEMI and NSTEMI/UA patients separately. In addition, we also studied the effect of these drugs among the patients managed with DES or BMS. We were also able to match P2Y12 inhibitors users on their propensity scores based on important clinical factors such as age categories, sex, region, plan types, comorbidity conditions, high bleeding risk, and previous medication history.

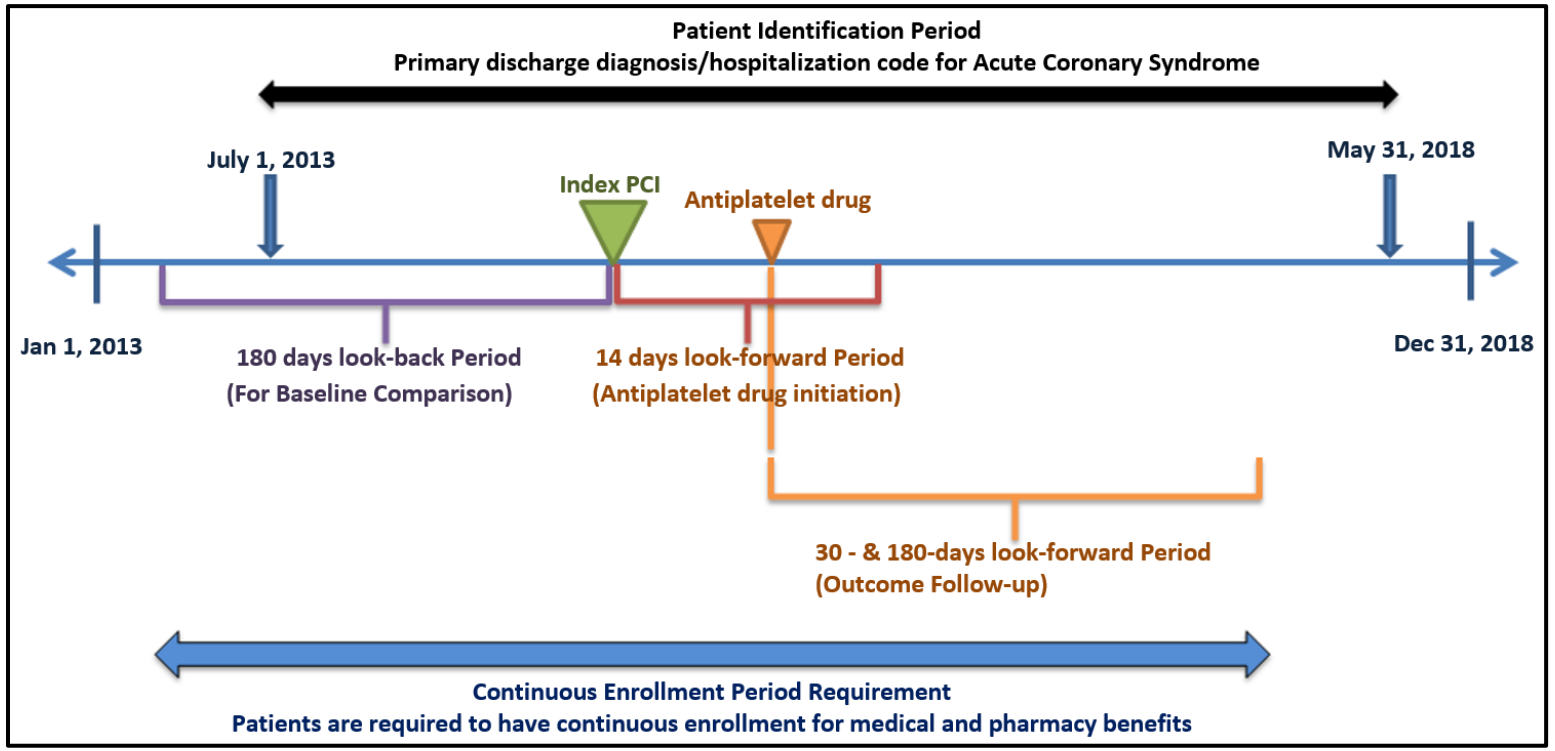
This study also has several limitations. Although various important clinical variables were used to control for the confounding, residual confounding may occur due to the observational nature of the study. Some misclassification was certainly present, despite using validated algorithms were to identify incident ACS events, comorbidities of interest, and outcomes. As a validated algorithm to identify recurrent ACS events was

not available, this may further augment the misclassification. Additionally, we were not able to study the role of aspirin on comparative effectiveness of P2Y12 inhibitors as MarketScan data does not reliably capture over-the-counter medications. Finally, we did not have access to patients' laboratory values, socioeconomic status, race, ethnicity, and formulary preference which might act as confounders or have helped in determination of ACS type.

4.5. Conclusion

In this study, we found that ticagrelor and prasugrel were not associated with a lower incidence of composite cardiovascular outcomes compared to clopidogrel among patients undergoing PCI. Additionally, use of newer agents was not associated with better effectiveness in terms of reduction of ischemic/hemorrhagic stroke, recurrent ACS, heart failure, and PAD events individually. The results of this study, however, indicate better effectiveness associated with newer P2Y12 inhibitors in the female population. Nevertheless, we observed higher risk of bleeding with prasugrel compared to ticagrelor. Given the differential mechanism of ACS prognosis based on sex, future studies are warranted to confirm these finding by studying these drugs specifically in female population.

Figure 4. 1 Scheme for Patient Selection



Acronym: PCI: percutaneous coronary intervention

Table 4. 1 Number of Events in Each Group of P2Y12 Inhibitors Users before Propensity Score Matching

Number of events in each group before propensity score matching			
At 30 days			
Event	***Clopidogrel (N=42,720)***	***Ticagrelor (24,414)***	***Prasugrel (12,011)***
Composite cardiovascular events	1172 (2.74%)	598 (2.45%)	247 (2.06%)
Coronary Artery Disease	838 (1.96%)	491 (2.01%)	192 (1.60%)
Heart Failure	535 (1.25%)	222 (0.91%)	96 (0.80)
Stroke	52 (0.12%)	14 (0.06%)	8 (0.07%)
Peripheral Artery Disease	26 (0.06%)	10 (0.04%)	2 (0.02%)
At 180 days			
Event	***Clopidogrel (N=33,898)***	***Ticagrelor (N=18,588)***	***Prasugrel (N=9,744)***
Composite Cardiovascular Events	2431 (7.17%)	1059 (5.70%)	498 (5.11%)
Coronary Artery Disease	1463 (4.32%)	739 (3.98%)	353 (3.62%)
Heart Failure	1342 (3.96%)	500 (2.69%)	216 (2.22%)
Stroke	121 (0.36%)	38 (0.20%)	20 (0.21%)
Peripheral Artery Disease	85 (0.25%)	33 (0.18%)	11 (0.11%)

Note: Composite cardiovascular events include hospitalizations due to cardiovascular, heart failure, or stroke events.

Table 4. 2 Comparative Risk of Composite Cardiovascular Outcomes (Primary Effectiveness Outcomes) before and after Propensity Score Matching

Variables	**Ticagrelor vs Clopidogrel** (Hazard Ratios (95% CI))	**Prasugrel vs Clopidogrel** (Hazard Ratios (95% CI))	**Ticagrelor vs Prasugrel** (Hazard Ratios (95% CI))
30 DAY-Overall Sample			
Before PS Matching			
Crude analysis	**0.89 (0.81 0.99)**	**0.75 (0.65 0.86)**	**0.84 (0.72 0.97)**
PS Matched Comparisons			
Primary Analysis	0.98 (0.87 1.11)	0.99 (0.83 1.18)	0.88 (0.74 1.05)
Subgroups			
Type of ACS			
STEMI	1.00 (0.85 1.19)	0.97 (0.77 1.21)	0.94 (0.75 1.18)
NSTEMI	0.94 (0.79 1.11)	1.08 (0.84 1.39)	0.98 (0.76 1.27)
Type of Stent			
BMS	0.93 (0.66 1.32)	0.85 (0.48 1.53)	0.70 (0.39 1.27)
DES	1.04 (0.89 1.22)	1.10 (0.87 1.39)	0.91 (0.73 1.14)
Sex			
Male	1.09 (0.94 1.26)	0.97 (0.79 1.19)	0.85 (0.69 1.04)
Female	**0.80 (0.65 0.98)**	1.05 (0.76 1.46)	0.96 (0.69 1.34)
180 DAY-Overall Sample			
Before PS Matching			
Crude Outcome	**0.79 (0.74 0.85)**	**0.71 (0.64 0.78)**	**0.89 (0.80 0.99)**
PS Matched Comparisons			
Primary Analysis	0.99 (0.90 1.08)	0.96 (0.85 1.08)	0.95 (0.84 1.08)
	Subgroups		
Type of ACS			
STEMI	0.99 (0.87 1.13)	0.97 (0.81 1.15)	0.93 (0.78 1.10)
NSTEMI	1.06 (0.94 1.20)	1.04 (0.87 1.24)	0.98 (0.82 1.18)
Type of Stent			
BMS	0.92 (0.70 1.20)	0.84 (0.55 1.27)	0.69 (0.45 1.08)
DES	1.03 (0.91 1.16)	0.95 (0.81 1.13)	0.90 (0.77 1.07)
Gender			
Males	1.02 (0.92 1.14)	0.93 (0.80 1.08)	0.89 (0.77 1.04)
Females	0.91 (0.78 1.07)	1.01 (0.81 1.26)	1.10 (0.87 1.38)

Acronyms: PS: propensity score**,** ACS: acute coronary syndrome, STEMI: ST wave elevated myocardial infarction, NSTEMI: non-ST elevated myocardial infarction, UA: unstable angina, BMS: bare-metal stents, DES: drug eluting stents

Note: Overall sample includes combined CCAE and MDCR datasets

Table 4. 3 Comparative Risk of Composite Cardiovascular Outcomes (Primary Effectiveness Outcomes) before and after Propensity Score Matching (Sensitivity Analysis: CCAE Sample)

Variables	**Clopidogrel vs Ticagrelor** (Hazard Ratios (95% CI))	**Clopidogrel vs Prasugrel** (Hazard Ratios (95% CI))	**Ticagrelor vs Prasugrel** (Hazard Ratios (95% CI))
30 DAY- CCAE Sample			
Before PS Matching			
Crude Outcome	0.92 (0.82 1.03)	**0.75 (0.64 0.87)**	**0.81 (0.69 0.95)**
PS Matched Comparisons			
Primary Analysis	1.00 (0.88 1.15))	0.87 (0.72 1.04)	0.90 (0.74 1.09)
Sub Groups			
Type of ACS	1.00 (0.88 1.15)	0.87 (0.72 1.04)	0.90 (0.74 1.09)
STEMI	0.94 (0.79 1.13)	0.89 (0.70 1.13)	0.93 (0.73 1.18)
NSTEMI	1.09 (0.89 1.33)	0.89 (0.68 1.16)	1.00 (0.75 1.34)
Type of Stent			
BMS	0.89 (0.59 1.35)	0.87 (0.44 1.73)	0.54 (0.28 1.03)
DES	1.03 (0.87 1.22)	0.93 (0.73 1.18)	0.96 (0.75 1.22)
Gender			
Males	1.04 (0.89 1.23)	0.97 (0.78 1.21)	0.87 (0.69 1.08)
Females	0.92 (0.73 1.17)	**0.67 (0.48 0.94)**	1.01 (0.69 1.47)
180 DAY- CCAE Sample			
Before PS Matching			
Crude Outcome	**0.87 (0.80 0.95)**	**0.79 (0.71 0.89)**	0.91 (0.80 1.03)
PS Matched Comparisons			
Primary Analysis	0.99 (0.89 1.10)	0.91 (0.79 1.04)	0.95 (0.82 1.09)
Sub Groups			
Type of ACS			
STEMI	0.99 (0.86 1.15)	0.89 (0.74 1.07)	0.88 (0.73 1.07)
NSTEMI	1.14 (0.98 1.33)	0.98 (0.80 1.19)	0.96 (0.77 1.18)
Type of Stent			
BMS	1.06 (0.77 1.46)	0.68 (0.42 1.09)	**0.57 (0.35 0.95)**
DES	1.03 (0.89 1.18)	0.91 (0.76 1.10)	0.89 (0.74 1.07)
Gender			
Males	1.01 (0.89 1.15)	0.91 (0.77 1.07)	0.89 (0.75 1.05)
Females	0.93 (0.76 1.13)	0.90 (0.70 1.16)	1.11 (0.85 1.45)

Acronyms: PS: propensity score**,** ACS: acute coronary syndrome, STEMI: ST wave elevated myocardial infarction, NSTEMI: non-ST elevated myocardial infarction, UA: unstable angina, BMS: bare-metal stents, DES: drug eluting stents

Table 4. 4 Comparative Risk of Composite Cardiovascular Outcomes (Primary Effectiveness Outcomes) before and after Propensity Score Matching (Sensitivity Analysis: MDCR Sample)

Variables	**Clopidogrel vs Ticagrelor** (Hazard Ratios (95% CI))	**Clopidogrel vs Prasugrel** (Hazard Ratios (95% CI))	**Ticagrelor vs Prasugrel** (Hazard Ratios (95% CI))
30 DAY-MDCR Sample			
Before PS Matching			
Crude Outcome	**0.77 (0.62 0.96)**	0.74 (0.53 1.04)	0.96 (0.66 1.41)
PS Matched Comparisons			
Primary Analysis	1.13 (0.85 1.51)	0.95 (0.60 1.49)	0.89 (0.56 1.42)
Sub Groups			
Type of ACS			
STEMI	1.16 (0.72 1.87)	1.25 (0.62 2.50)	1.21 (0.62 2.36)
NSTEMI	0.89 (0.61 1.29)	0.89 (0.50 1.58)	1.06 (0.57 1.97)
Type of Stent			
BMS	1.58 (0.70 3.57)	1.95 (0.52 7.27)	1.71 (0.46 6.37)
DES	0.91 (0.59 1.39)	0.76 (0.41 1.43)	1.22 (0.59 2.54)
Gender			
Males	1.22 (0.83 1.78)	0.82 (0.47 1.44)	0.65 (0.37 1.17)
Females	1.01 (0.64 1.59)	1.23 (0.57 2.62)	1.67 (0.73 3.81)
180 DAY-MDCR Sample			
Before PS Matching			
Crude Outcome	**0.83 (0.73 0.94)**	**0.79 (0.65 0.96)**	0.96 (0.77 1.19)
PS Matched Comparisons			
Primary Analysis	1.03 (0.88 1.22)	1.05 (0.79 1.39)	1.14 (0.86 1.51)
Sub Groups			
Type of ACS			
STEMI	0.96 (0.73 1.27)	1.10 (0.73 1.65)	1.27 (0.84 1.93)
NSTEMI	1.03 (0.83 1.26)	1.22 (0.84 1.78)	1.31 (0.91 1.89)
Type of Stent			
BMS	1.06 (0.61 1.85)	1.23 (0.54 2.81)	1.23 (0.45 3.39)
DES	1.12 (0.89 1.42)	0.99 (0.66 1.48)	0.92 (0.63 1.33)
Gender			
Males	1.08 (0.87 1.33)	0.94 (0.67 1.32)	0.93 (0.67 1.30)
Females	0.98 (0.76 1.26)	1.34 (0.80 2.23)	**1.84 (1.08 3.12)**

Acronyms: PS: propensity score**,** ACS: acute coronary syndrome, STEMI: ST wave elevated myocardial infarction, NSTEMI: non-ST elevated myocardial infarction, UA: unstable angina, BMS: bare-metal stents, DES: drug eluting stents

Table 4. 5 Number of Events, Cumulative Incidence, Absolute Risk Difference, and Number Needed to Treat for Composite Cardiovascular Outcomes in 1:1 PS Matched Comparisons

P2Y12 inhibitor	Number of events	Total number of patients	Cumulative Incidence	Person Days	% Absolute Risk Difference (%ARR)	The number needed to treat (NNT) (1/ ARR)
Composite Cardiovascular Outcome						
30 days outcomes PS Matched Comparisons						
	Clopidogrel versus Ticagrelor (PS Match (1:1))					
Clopidogrel	545	21549	0.025291197	635890	0.041765279	2,394
Ticagrelor	536	21549	0.024873544	635930		
	Clopidogrel versus Prasugrel (PS Match (1:1))					
Clopidogrel	248	11776	0.021059783	348718	0.016983696	5,887
Prasugrel	246	11776	0.020889946	348723		
	Ticagrelor versus Prasugrel (PS Match (1:1))					
Ticagrelor	271	11263	0.024061085	332682	0.284116132	351
Prasugrel	239	11263	0.021219924	333513		
180 days outcomes PS Matched Comparisons						
	Clopidogrel versus Ticagrelor (PS Match (1:1))					
Clopidogrel	996	16880	0.059004739	2924296	0.071090047	1406
Ticagrelor	984	16880	0.058293839	2927142		
	Clopidogrel versus Prasugrel (PS Match (1:1))					
Clopidogrel	515	9615	0.053562142	1670458	0.218408736	457
Prasugrel	494	9615	0.051378055	1674072		
	Ticagrelor versus Prasugrel (PS Match (1:1))					
Ticagrelor	499	9130	0.054654984	1586868	-0.26286966	380
Prasugrel	475	9130	0.052026287	1588838		

Note: PSMATCH (1:1)- Propensity score matching (1:1) with nearest-neighbor matching technique without replacement

4.6. Supplementary Materials

Appendix Table 4. 1 ICD 9 & 10 CM and CPT Codes for Identification of Events and Outcomes

Cohort Selection	
Acute Coronary Syndrome (Any Position)	**Acute Myocardial Infarction:** **ICD-9 CM:** 410, 410.0, 410.00, 410.01, 410.1, 410.10, 410.11, 410.2, 410.20, 410.21, 410.3, 410.30, 410.31, 410.4, 410.40, 410.41, 410.5, 410.50, 410.51, 410.6, 410.60, 410.61, 410.7, 410.70, 410.71, 410.8, 410.80, 410.81, 410.9, 410.90, 410.91 **ICD-10 CM:** I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I21.4, R9430, R9431 **Unstable Angina:** **ICD-9 CM:** 411, 411.0, 411.1, 411.8, 411.81, 411.89 **ICD-10 CM:**: I20.0, I24, I24.0, I24.1, I24.8, I24.9, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790
Percutaneous Coronary Intervention (PCI) (Any position):	**ICD 9 Procedure codes:** '0066' '3601' '3602' '3603' '3605' '3606' '3607' '3609' **ICD 10 Procedure codes:** '0270346' '027034Z' '0270356' '027035Z' '0270366' '027036Z' '0270376' '027037Z' '02703D6' '02703DZ' '02703ZZ' '0270046' '0271346' '027134Z' '0271356' '027135Z' '0271366' '027136Z' '0271376' '027137Z' '02713D6' '02713DZ' '02714E6' '02713EZ' '02714EZ' '02723FZ' '02733GZ' '02713E6' '02723F6' '02733G6' '0272366' '0273376' '027236Z' '027337Z' '02C03ZZ' '02C13ZZ' '02C23ZZ' '02C33ZZ' '02C03Z6' '02C13Z6' '02C23Z6' '02C33Z6' '92980' '92981' '92982' '92984' '92920' '92924' '92925' '92921' '92928' '92929' '92933' '92934' '37184' '37185' '37186' '37187' '37188' 'C9600' 'C9601' 'C9602' 'C9603' 'G0290' 'G0291'
Outcomes Identification	
Myocardial Infarction (Any position):	**ICD-9 CM:** 410, 410.0, 410.00, 410.01, 410.1, 410.10, 410.11, 410.2, 410.20, 410.21, 410.3, 410.30, 410.31, 410.4, 410.40, 410.41, 410.5, 410.50, 410.51, 410.6, 410.60, 410.61, 410.7, 410.70, 410.71, 410.8, 410.80, 410.81, 410.9, 410.90, 410.91 **ICD-10 CM:** I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I21.4, I22.0, I22.1, I22.2, I22.8, I22.9
Unstable Angina (Any position):	**ICD-9 CM:** 411, 411.0, 411.1, 411.8, 411.81, 411.89 **ICD-10 CM:** I20.0, I24, I24.0, I24.1, I24.8, I24.9, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790
Revascularizations: (Any Position)	**PCI:** **ICD 9 Procedure codes:** '0066' '3601' '3602' '3603' '3605' '3606' '3607' '3609' **ICD 10 Procedure codes:** '0270346' '027034Z' '0270356' '027035Z' '0270366' '027036Z' '0270376' '027037Z' '02703D6' '02703DZ' '02703ZZ' '0270046' '0271346' '027134Z' '0271356' '027135Z'

	'0271366' '027136Z' '0271376' '027137Z' '02713D6' '02713DZ' '02714E6' '02713EZ' '02714EZ' '02723FZ' '02733GZ' '02713E6' '02723F6' '02733G6' '0272366' '0273376' '027236Z' '027337Z' '02C03ZZ' '02C13ZZ' '02C23ZZ' '02C33ZZ' '02C03Z6' '02C13Z6' '02C23Z6' '02C33Z6' '92980' '92981' '92982' '92984' '92920' '92924' '92925' '92921' '92928' '92929' '92933' '92934' '37184' '37185' '37186' '37187' '37188' 'C9600' 'C9601' 'C9602' 'C9603' 'G0290' 'G0291' **CABG:** **ICD 9 Procedure codes:** '361' '3610' '3611' '3612' '3613' '3614' '3615' '3616' '3617' '3619' '362' '0210' **ICD 10 Procedure codes:** '021009W' '02100A3' '02100A8' '02100A9' '02100AC' '02100AF' '02100AW' '33510' '33511' '33512' '33513' '33514' '33516' '33517' '33518' '33519' '33520' '33521' '33522' '33523' '33530' '33533' '33534' '33535' '33536' '33545' '92937' '92938' 'C9604' 'C9605' 'C9606' **Fibrinolysis:** **ICD 9 Procedure codes:** '9910' '3604' **ICD 10 Procedure codes:** '3E07' '3E07017' '3E07317' '3E07017' '3E07317' '3E08017' '3E08317' 'J2993' 'J2995' 'J2997' 'J0350' 'J3101' '32561' '32562' '86590' '36593'
STROKE (Primary Position Only)	**Primary inpatient discharge diagnosis (ICD-9):** **ICD-9 CM**: 430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436 **ICD-10 CM** I60.00, I60.01, I60.02, I60.10, I60.11, I60.12, I60.2, I60.30, I60.31, I60.32, I60.4, I60.50, I60.51, I60.52, I60.6, I60.7, I60.8, I60.9, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I63.00, I63.011, I63.012, I63.019, I63.02, I63.031, I63.032, I63.039, I63.09, I63.10, I63.111, I63.112, I63.119, I63.12, I63.131, I63.132, I63.139, I63.19, I63.20, I63.211, I63.212, I63.219, I63.22, I63.231, I63.232, I63.239, I63.29, I63.30, I63.311, I63.312, I63.319, I63.321, I63.322, I63.329, I63.331, I63.332, I63.339, I63.341, I63.342, I63.349, I63.39, I63.40, I63.411, I63.412, I63.419, I63.421, I63.422, I63.429, I63.431, I63.432, I63.439, I63.441, I63.442, I63.449, I63.49, I63.50, I63.511, I63.512, I63.519, I63.521, I63.522, I63.529, I63.531, I63.532, I63.539, I63.541, I63.542, I63.549, I63.59, I63.6, I63.8, I63.9, I67.89
Trans Ischemic Attack (Primary Position Only)	**ICD-9 CM:** 435.0 435.1 435.2 435.3 435.8 435.9 **ICD 10 CM:** G45.0, G45.1, G45.2, G45.8, G45.9
Heart Failure (Any position):	**ICD-9 diagnosis:** 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, 428.0, 428.1, 428.2, 428.20, 428.21, 428.22, 428.23, 428.3, 428.30, 428.31, 428.32, 428.33, 428.4, 428.40, 428.41, 428.42, 428.43, 428.9 **ICD-10 diagnosis:** I09.81, I11.0, I13.0, I13.2, I50, I50.1, I50.2, I50.20, I50.21, I50.22, I50.23, I50.3, I50.30, I50.31, I50.32, I50.33, I50.4, I50.40, I50.41, I50.42, I50.43, I50.8, I50.81,

	I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9
Peripheral Artery Disease	**Acute limb ischemia (Primary Position Only):** **ICD 9 CM:** 444.0, 444.01, 444.09, 444.22, 444.81. **ICD10 CM:** I74.01, I74.09, I74.3, I74.5. **CPT procedure codes for embolectomy or thrombectomy (Any Position):** 34201, 34203. **ICD9 procedure codes for peripheral surgical revascularization (Any Position):** 38.08, 38.16, 38.18, 38.38, 38.48, 38.68, 38.88, 39.25, 39.29. **ICD10 procedure codes for peripheral surgical revascularization (Any Position)**: 0312096, 0312097, 0312098, 0312099, 031209B, 031209C, 03120A6, 03120A7, 03120A8, 03120A9, 03120AB, 03120AC, 03120J6, 03120J7, 03120J8, 03120J9, 03120JB, 03120JC, 03120K6, 03120K7, 03120K8, 03120K9, 03120KB, 03120KC, 03120Z6, 03120Z7, 03120Z8, 03120Z9, 03120ZB, 03120ZC, 031309B, 031309C, 03130A6, 03130A7, 03130A8, 03130A9, 03130AB, 03130AC, 03130J6, 03130J7, 03130J8, 03130J9, 03130JB, 03130JC, 03130K6, 03130K7, 03130K8, 03130K9, 03130KB, 03130KC, 03130Z6, 03130Z7, 03130Z8, 03130Z9, 03130ZB, 03130ZC, 0314096, 0314097, 0314098, 0314099, 031409B, 031409C, 03140A6, 03140A7, 03140A8, 03140A9, 03140AB, 03140AC, 03140J6, 03140J7, 03140J8, 03140J9, 03140JB, 03140JC, 03140K6, 03140K7, 03140K8, 03140K9, 03140KB, 03140KC, 03140Z6, 03140Z7, 03140Z8, 03140Z9, 03140ZB, 03140ZC, 0315096, 0315097, 0315098, 0315099, 031509B, 031509C, 03150A6, 03150A7, 03150A8, 03150A9, 03150AB, 03150AC, 03150J6, 03150J7, 03150J8, 03150J9, 03150JB, 03150JC, 03150K6, 03150K7, 03150K8, 03150K9, 03150KB, 03150KC, 03150Z6, 03150Z7, 03150Z8, 03150Z9, 03150ZB, 03150ZC, 0316096, 0316097, 0316098, 0316099, 031609B, 031609C, 03160A6, 03160A7, 03160A8, 03160A9, 03160AB, 03160AC, 03160J6, 03160J7, 03160J8, 03160J9, 03160JB, 03160JC, 03160K6, 03160K7, 03160K8, 03160K9, 03160KB, 03160KC, 03160Z6, 03160Z7, 03160Z8, 03160Z9, 03160ZB, 03160ZC, 0410096, 0410097, 0410098, 0410099, 041009B, 041009C, 041009D, 041009F, 041009G, 041009H, 041009J, 041009K, 041009Q, 041009R, 04100A6, 04100A7, 04100A8, 04100A9, 04100AB, 04100AC, 04100AD, 04100AF, 04100AG, 04100AH, 04100AJ, 04100AK, 04100AQ, 04100AR, 04100J6, 04100J7, 04100J8, 04100J9, 04100JB, 04100JC, 04100JD, 04100JF, 04100JG, 04100JH, 04100JJ, 04100JK, 04100JQ, 04100JR, 04100K6, 04100K7, 04100K8, 04100K9, 04100KB, 04100KC, 04100KD, 04100KF, 04100KG, 04100KH, 04100KJ, 04100KK, 04100KQ, 04100KR, 04100Z6, 04100Z7, 04100Z8, 04100Z9, 04100ZB, 04100ZC, 04100ZD, 04100ZF, 04100ZG, 04100ZH, 04100ZJ, 04100ZK, 04100ZQ, 04100ZR, 0410496, 0410497, 0410498, 0410499, 041049B, 041049C, 041049D, 041049F, 041049G, 041049H, 041049J, 041049K, 041049Q, 041049R, 04104A6, 04104A7, 04104A8, 04104A9, 04104AB, 04104AC, 04104AD, 04104AF, 04104AG, 04104AH,

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	04RY07Z, 04RY0JZ, 04RY0KZ, 04RY47Z, 04RY4JZ, 04RY4KZ, 04WY0YZ, 04WY3YZ, 04WY4YZ, 313096, 313097, 313098, 313099. **CPT procedure codes for peripheral surgical revascularization (Any Position):** 35302, 35303, 35304, 35305, 35351, 35355, 35361, 35363, 35371, 35372, 35381, 35480, 35481, 35482, 35483, 35485, 35521, 35537, 35538, 35539, 35540, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35570, 35571, 35583, 35585, 35587, 35621, 35623, 35641, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 35875, 35876.
STEMI, NSTEMI/UA (First Two Positions)	**STEMI:** **ICD-9 CM:** 410, 410.0, 410.00, 410.01, 410.1, 410.10, 410.11, 410.2, 410.20, 410.21, 410.3, 410.30, 410.31, 410.4, 410.40, 410.41, 410.5, 410.50, 410.51, 410.6, 410.60, 410.61, 410.8, 410.80, 410.81, 410.9, 410.90, 410.91 **ICD-10 CM:** I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, R9430, R9431 **NSTEMI/UA:** **ICD-9 CM:** 411, 411.0, 411.1, 411.8, 411.81, 411.89, 410.7, 410.70, 410.71, **ICD-10 CM:** I20.0, I21.4, I24, I24.0, I24.1, I24.8, I24.9, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790

Acronyms: ICD 9 & 10 CM codes**:** international classification of disease 9 & 10 clinical modification codes, CPT: current diagnosis procedure codes, STEMI: ST-wave elevated myocardial infarction; NSTEMI: Non-ST-wave elevated myocardial infarction; UA: Unstable Angina

Appendix Table 4. 2 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users before Propensity Score Matching: MarketScan 2013-2018

Variable	30 Day			180 Day		
	Clopidogrel N = 42,720	Ticagrelor N = 24,414	Prasugrel N = 12,011	Clopidogrel N = 33,898	Ticagrelor N = 18,588	Prasugrel N = 9,744
AGE CATEGORY						
18-44 Years	2,242 (5.2%)	1,873 (7.7%)	994 (8.3%)	1,757 (5.2%)	1,366 (7.3%)	795 (8.2%)
45-64 Years	25,255 (59.1%)	17,821 (73%)	9,174 (76.4%)	19,932 (58.8%)	13,487 (72.6%)	7,494 (76.9%)
65-84 Years	13,052 (30.6%)	4,353 (17.8%)	1,798 (15%)	10,470 (30.9%)	3,430 (18.5%)	1,419 (14.6%)
85 Years & Above	2,171 (5.1%)	367 (1.5%)	45 (0.4%)	1,739 (5.1%)	305 (1.6%)	36 (0.4%)
SEX						
Male	29,991 (70.2%)	18,258 (74.8%)	9,358 (77.9%)	23,862 (70.4%)	13,926 (74.9%)	7,614 (78.1%)
Female	12,729 (29.8%)	6,156 (25.2%)	2,653 (22.1%)	10,036 (29.6%)	4,662 (25.1%)	2,130 (21.9%)
REGION						
Northeast	8,614 (20.2%)	4,978 (20.4%)	2,009 (16.7%)	6,890 (20.3%)	3,854 (20.7%)	1,632 (16.7%)
North Central	12,286 (28.8%)	6,186 (25.3%)	2,548 (21.2%)	9,863 (29.1%)	4,797 (25.8%)	2,132 (21.9%)
South	15,733 (36.8%)	10,547 (43.2%)	5,759 (47.9%)	12,515 (36.9%)	7,951 (42.8%)	4,698 (48.2%)
West	5,707 (13.4%)	2,549 (10.4%)	1,530 (12.7%)	4,371 (12.9%)	1,876 (10.1%)	1,177 (12.1%)
Other	380 (0.9%)	154 (0.6%)	165 (1.4%)	259 (0.8%)	110 (0.6%)	105 (1.1%)
PLAN TYPE						
Comprehensive	7,437 (17.4%)	2,300 (9.4%)	1,180 (9.8%)	6,202 (18.3%)	1,841 (9.9%)	996 (10.2%)
EPO	305 (0.7%)	207 (0.8%)	107 (0.9%)	231 (0.7%)	151 (0.8%)	82 (0.8%)
HMO	4,641 (10.9%)	2,313 (9.5%)	1,132 (9.4%)	3,522 (10.4%)	1,761 (9.5%)	880 (9%)
POS	2,476 (5.8%)	1,597 (6.5%)	751 (6.3%)	1,911 (5.6%)	1,109 (6%)	609 (6.3%)
PPO	22,091 (51.7%)	13,185 (54%)	6,796 (56.6%)	17,607 (51.9%)	10,113 (54.4%)	5,542 (56.9%)
POS with Capitation	384 (0.9%)	265 (1.1%)	80 (0.7%)	301 (0.9%)	207 (1.1%)	63 (0.6%)
CDHP	2,835 (6.6%)	2,542 (10.4%)	1,086 (9%)	2,343 (6.9%)	1,998 (10.7%)	941 (9.7%)
HDHP	1,779 (4.2%)	1,509 (6.2%)	646 (5.4%)	1,350 (4%)	1,116 (6%)	506 (5.2%)
ELIXHAUSER INDEX						
Category 0	11,928 (27.9%)	7,788 (31.9%)	3,682 (30.7%)	9,555 (28.2%)	5,942 (32%)	2,993 (30.7%)

Variable	30 Day			180 Day		
	Clopidogrel N = 42,720	**Ticagrelor N = 24,414**	**Prasugrel N = 12,011**	**Clopidogrel N = 33,898**	**Ticagrelor N = 18,588**	**Prasugrel N = 9,744**
Category 1	10,859 (25.4%)	6,631 (27.2%)	3,744 (31.2%)	8,982 (26.5%)	5,260 (28.3%)	3,171 (32.5%)
Category 2	2,960 (6.9%)	1,815 (7.4%)	771 (6.4%)	2,310 (6.8%)	1,331 (7.2%)	607 (6.2%)
Category 3	9,335 (21.9%)	4,923 (20.2%)	2,504 (20.8%)	7,356 (21.7%)	3,667 (19.7%)	1,997 (20.5%)
Category 4	7,638 (17.9%)	3,257 (13.3%)	1,310 (10.9%)	5,695 (16.8%)	2,388 (12.8%)	976 (10%)
ACS TYPE						
STEMI	12,967 (30.4%)	9,275 (38%)	4,503 (37.5%)	10,402 (30.7%)	7,155 (38.5%)	3,697 (37.9%)
NSTEMI/UA	24,869 (58.2%)	12,751 (52.2%)	6,281 (52.3%)	19,766 (58.3%)	9,698 (52.2%)	5,110 (52.4%)
STENT TYPE						
DES	23,758 (55.6%)	15,517 (65.6%)	656 (5.5%)	18,610 (54.9%)	11662 (62.7%)	5820 (63.6%)
BMS	3397 (8.0%)	1,402 (5.7%)	7,300 (60.8%)	2,647 (7.8%)	1052 (5.7%)	533 (5.5%)
BLEEDING RISK						
High Bleeding Risk	19,371 (45.3%)	9,225 (37.8%)	4,381 (36.5%)	15,077 (44.5%)	6,875 (37%)	3,471 (35.6%)
MEDICATION HISTORY						
Anti-Diabetics						
Antidiabetics (Miscellaneous: *Biguanides, GLP-1 analogues DPP4, alpha-glucoside inhibitors, incretin mimetics, amylin analogues, glucagon, and combinations*)	7,467 (17.5%)	4,128 (16.9%)	2,074 (17.3%)	5,846 (17.2%)	3,098 (16.7%)	1,624 (16.7%)
Meglitinide	143 (0.3%)	56 (0.2%)	27 (0.2%)	110 (0.3%)	42 (0.2%)	22 (0.2%)
SGLT Inhibitors	630 (1.5%)	575 (2.4%)	224 (1.9%)	478 (1.4%)	406 (2.2%)	172 (1.8%)
Sulfnylureas	3,480 (8.1%)	1,638 (6.7%)	797 (6.6%)	2,726 (8%)	1,230 (6.6%)	622 (6.4%)
TZDs	472 (1.1%)	264 (1.1%)	145 (1.2%)	367 (1.1%)	200 (1.1%)	117 (1.2%)
Anti-Hypertensive						
ACE Inhibitors	10,727 (25.1%)	5,308 (21.7%)	2,735 (22.8%)	8,491 (25%)	4,007 (21.6%)	2,191 (22.5%)
Beta Blockers	16,076 (37.6%)	6,867 (28.1%)	3,610 (30.1%)	12,638 (37.3%)	5,229 (28.1%)	2,874 (29.5%)

Variable	30 Day			180 Day		
	Clopidogrel N = 42,720	Ticagrelor N = 24,414	Prasugrel N = 12,011	Clopidogrel N = 33,898	Ticagrelor N = 18,588	Prasugrel N = 9,744
Calcium Channel Blockers	9,144 (21.4%)	4,241 (17.4%)	1,911 (15.9%)	7,198 (21.2%)	3,240 (17.4%)	1,498 (15.4%)
ARBs	8,071 (18.9%)	4,233 (17.3%)	2,005 (16.7%)	6,368 (18.8%)	3,242 (17.4%)	1,599 (16.4%)
Diuretics						
Loop Diuretics	4,040 (9.5%)	1,199 (4.9%)	568 (4.7%)	3,096 (9.1%)	903 (4.9%)	444 (4.6%)
Potassium Sparing Diuretics	1,754 (4.1%)	657 (2.7%)	348 (2.9%)	1,344 (4%)	497 (2.7%)	280 (2.9%)
Thiazide Diuretics	3,418 (8%)	1,620 (6.6%)	793 (6.6%)	2,729 (8.1%)	1,198 (6.4%)	618 (6.3%)
Other Medications						
Anti-Platelets	4,900 (11.5%)	2,228 (9.1%)	1,325 (11%)	3,798 (11.2%)	1,661 (8.9%)	998 (10.2%)
Anti-Arrhythmics	740 (1.7%)	163 (0.7%)	90 (0.7%)	546 (1.6%)	125 (0.7%)	67 (0.7%)
Anti-Hyperlipidimics	20,368 (47.7%)	10,160 (41.6%)	5,309 (44.2%)	16,064 (47.4%)	7,697 (41.4%)	4,256 (43.7%)
Anti-Depressants	7,822 (18.3%)	4,005 (16.4%)	1,984 (16.5%)	6,058 (17.9%)	2,993 (16.1%)	1,592 (16.3%)
Estrogens	770 (1.8%)	372 (1.5%)	208 (1.7%)	606 (1.8%)	296 (1.6%)	163 (1.7%)
PPIs	9,084 (21.3%)	4,376 (17.9%)	2,207 (18.4%)	7,131 (21%)	3,331 (17.9%)	1,729 (17.7%)
H2RAs	1,438 (3.4%)	665 (2.7%)	277 (2.3%)	1,132 (3.3%)	510 (2.7%)	220 (2.3%)

Acronyms: EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 4. 3 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users before Propensity Score Matching for the MarketScan Commercial Claims and Encounters Database (CCAE) Sample Sensitivity Analysis): MarketScan 2013-2018

	30 Days			180 Days		
Variable	Clopidogrel N = 27,568	Ticagrelor N = 19,759	Prasugrel N = 10,187	Clopidogrel N = 21,689	Ticagrelor N = 14,853	Prasugrel N = 8,289
AGE CATEGORY						
18-45 Years	2,707 (9.8%)	2,250 (11.4%)	1,202 (11.8%)	2,135 (9.8%)	1,651 (11.1%)	976 (11.8%)
46-55 Years	9,191 (33.3%)	7,095 (35.9%)	3,676 (36.1%)	7,365 (34%)	5,441 (36.6%)	3,066 (37%)
56-65 Years	15,670 (56.8%)	10,414 (52.7%)	5,309 (52.1%)	12,189 (56.2%)	7,761 (52.3%)	4,247 (51.2%)
SEX						
Male	20,653 (74.9%)	15,300 (77.4%)	8,041 (78.9%)	16,336 (75.3%)	11,552 (77.8%)	6,566 (79.2%)
Female	6,915 (25.1%)	4,459 (22.6%)	2,146 (21.1%)	5,353 (24.7%)	3,301 (22.2%)	1,723 (20.8%)
REGION						
Northeast	5,105 (18.5%)	3,831 (19.4%)	1,613 (15.8%)	4,046 (18.7%)	2,910 (19.6%)	1,312 (15.8%)
North Central	6,824 (24.8%)	4,631 (23.4%)	2,003 (19.7%)	5,371 (24.8%)	3,545 (23.9%)	1,667 (20.1%)
South	11,361 (41.2%)	9,067 (45.9%)	5,111 (50.2%)	8,987 (41.4%)	6,771 (45.6%)	4,186 (50.5%)
West	3,943 (14.3%)	2,099 (10.6%)	1,313 (12.9%)	3,053 (14.1%)	1,538 (10.4%)	1,030 (12.4%)
Other	335 (1.2%)	131 (0.7%)	147 (1.4%)	232 (1.1%)	89 (0.6%)	94 (1.1%)
PLAN TYPE						
Comprehensive	1,314 (4.8%)	514 (2.6%)	495 (4.9%)	1,094 (5%)	383 (2.6%)	420 (5.1%)
EPO	269 (1%)	182 (0.9%)	100 (1%)	205 (0.9%)	132 (0.9%)	78 (0.9%)
HMO	2,958 (10.7%)	1,878 (9.5%)	933 (9.2%)	2,273 (10.5%)	1,416 (9.5%)	736 (8.9%)
POS	1,905 (6.9%)	1,426 (7.2%)	673 (6.6%)	1,451 (6.7%)	977 (6.6%)	549 (6.6%)
PPO	15,815 (57.4%)	11,167 (56.5%)	6,001 (58.9%)	12,582 (58%)	8,502 (57.2%)	4,912 (59.3%)
POS with Capitation	220 (0.8%)	188 (1%)	64 (0.6%)	169 (0.8%)	152 (1%)	49 (0.6%)
CDHP	2,720 (9.9%)	2,477 (12.5%)	1,065 (10.5%)	2,259 (10.4%)	1,945 (13.1%)	927 (11.2%)
HDHP	1,732 (6.3%)	1,480 (7.5%)	639 (6.3%)	1,317 (6.1%)	1,092 (7.4%)	501 (6%)
ELIXHAUSER INDEX						

Variable	30 Days			180 Days		
	Clopidogrel N = 27,568	**Ticagrelor N = 19,759**	**Prasugrel N = 10,187**	**Clopidogrel N = 21,689**	**Ticagrelor N = 14,853**	**Prasugrel N = 8,289**
Category 0	8,280 (30%)	6,512 (33%)	3,180 (31.2%)	6,533 (30.1%)	4,933 (33.2%)	2,581 (31.1%)
Category 1	7,858 (28.5%)	5,642 (28.6%)	3,321 (32.6%)	6,439 (29.7%)	4,434 (29.9%)	2,815 (34%)
Category 2	1,997 (7.2%)	1,479 (7.5%)	672 (6.6%)	1,545 (7.1%)	1,078 (7.3%)	526 (6.3%)
Category 3	5,781 (21%)	3,885 (19.7%)	2,037 (20%)	4,486 (20.7%)	2,819 (19%)	1,631 (19.7%)
Category 4	3,652 (13.2%)	2,241 (11.3%)	977 (9.6%)	2,686 (12.4%)	1,589 (10.7%)	736 (8.9%)
ACS TYPE						
STEMI	9,289 (33.7%)	7,771 (39.3%)	3,966 (38.9%)	7,434 (34.3%)	5,926 (39.9%)	3,265 (39.4%)
NSTEMI/UA	15,423 (55.9%)	10,169 (51.5%)	5,234 (51.4%)	12,102 (55.8%)	7,624 (51.3%)	4,271 (51.5%)
STENT TYPE						
DES	15,169 (55.0%)	5,987 (30.3%)	2,072 (20.3%)	12,099 (55.8%)	4,819 (33.0%)	1,666 (20.1%)
BMS	2,909 (10.6%)	771 (3.9%)	217 (2.1%)	2,336 (10.8%)	621 (4.2%)	171 (2.1%)
HIGH BLEEDING RISK						
High Bleeding Risk	11,120 (40.3%)	7,050 (35.7%)	3,524 (34.6%)	8,517 (39.3%)	5,140 (34.6%)	2,798 (33.8%)
MEDICATION HISTORY						
Anti-Diabetics						
Antidiabetics (Miscellaneous: *Biguanides, GLP-1 analogues DPP4, alpha-glucoside inhibitors, incretin mimetics, amylin analogues, glucagon, and combinations*)	4,617 (16.7%)	3,207 (16.2%)	1,703 (16.7%)	3,571 (16.5%)	2,347 (15.8%)	1,335 (16.1%)
Meglitinide	53 (0.2%)	30 (0.2%)	18 (0.2%)	37 (0.2%)	22 (0.1%)	14 (0.2%)
SGLT Inhibitors	515 (1.9%)	510 (2.6%)	209 (2.1%)	389 (1.8%)	361 (2.4%)	160 (1.9%)
Sulfnylureas	1,908 (6.9%)	1,188 (6%)	610 (6%)	1,466 (6.8%)	860 (5.8%)	476 (5.7%)
TZDs	270 (1%)	208 (1.1%)	110 (1.1%)	204 (0.9%)	152 (1%)	83 (1%)
Anti-hypertensive						
ACE Inhibitors	6,433 (23.3%)	4,084 (20.7%)	2,228 (21.9%)	5,044 (23.3%)	3,043 (20.5%)	1,775 (21.4%)

Variable	30 Days			180 Days		
	Clopidogrel N = 27,568	Ticagrelor N = 19,759	Prasugrel N = 10,187	Clopidogrel N = 21,689	Ticagrelor N = 14,853	Prasugrel N = 8,289
Beta Blockers	8,443 (30.6%)	4,833 (24.5%)	2,797 (27.5%)	6,520 (30.1%)	3,615 (24.3%)	2,223 (26.8%)
Calcium Channel Blockers	4,552 (16.5%)	2,934 (14.8%)	1,455 (14.3%)	3,511 (16.2%)	2,190 (14.7%)	1,134 (13.7%)
ARBs	4,328 (15.7%)	3,105 (15.7%)	1,580 (15.5%)	3,343 (15.4%)	2,326 (15.7%)	1,261 (15.2%)
Diuretics						
Loop Diuretics	1,499 (5.4%)	642 (3.2%)	373 (3.7%)	1,101 (5.1%)	461 (3.1%)	293 (3.5%)
Potassium Sparing Diuretics	862 (3.1%)	442 (2.2%)	253 (2.5%)	649 (3%)	316 (2.1%)	201 (2.4%)
Thiazide Diuretics	1,882 (6.8%)	1,166 (5.9%)	627 (6.2%)	1,495 (6.9%)	841 (5.7%)	484 (5.8%)
Other Medications						
Anti-Platelets	2,633 (9.6%)	1,539 (7.8%)	1,026 (10.1%)	1,988 (9.2%)	1,117 (7.5%)	769 (9.3%)
Anti-Arrhythmics	273 (1%)	79 (0.4%)	61 (0.6%)	198 (0.9%)	56 (0.4%)	47 (0.6%)
Anti-Hyperlipidimics	11,438 (41.5%)	7,532 (38.1%)	4,230 (41.5%)	8,890 (41%)	5,591 (37.6%)	3,387 (40.9%)
Anti-Depressants	4,912 (17.8%)	3,219 (16.3%)	1,669 (16.4%)	3,753 (17.3%)	2,365 (15.9%)	1,354 (16.3%)
Estrogens	426 (1.5%)	275 (1.4%)	175 (1.7%)	331 (1.5%)	212 (1.4%)	137 (1.7%)
PPIs	4,872 (17.7%)	3,223 (16.3%)	1,753 (17.2%)	3,750 (17.3%)	2,414 (16.3%)	1,373 (16.6%)
H2RAs	664 (2.4%)	435 (2.2%)	196 (1.9%)	518 (2.4%)	320 (2.2%)	153 (1.8%)

Acronyms: EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 4. 4 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users before Propensity Score Matching for the Medicare Supplemental and Coordination of Benefits (MDCR) Sample (Sensitivity Analysis): MarketScan 2013-2018

	30 day			180 day		
Variable	**Clopidogrel N = 15,168**	**Ticagrelor N = 4,663**	**Prasugrel N = 1,830**	**Clopidogrel N = 12,218**	**Ticagrelor N = 3,740**	**Prasugrel N = 1,458**
AGE CATEGORY						
65-74 Years	6,850 (45.2%)	2,653 (56.9%)	1,423 (77.8%)	5,464 (44.7%)	2,109 (56.4%)	1,127 (77.3%)
75-84 Years	6,147 (40.5%)	1,643 (35.2%)	362 (19.8%)	5,015 (41%)	1,326 (35.5%)	295 (20.2%)
85 Years & Above	2,171 (14.3%)	367 (7.9%)	45 (2.5%)	1,739 (14.2%)	305 (8.2%)	36 (2.5%)
SEX						
Male	9,350 (61.6%)	2,964 (63.6%)	1,322 (72.2%)	7,533 (61.7%)	2,378 (63.6%)	1,051 (72.1%)
Female	5,818 (38.4%)	1,699 (36.4%)	508 (27.8%)	4,685 (38.3%)	1,362 (36.4%)	407 (27.9%)
REGION						
Northeast	3,517 (23.2%)	1,152 (24.7%)	396 (21.6%)	2,847 (23.3%)	948 (25.3%)	320 (21.9%)
North Central	5,468 (36%)	1,555 (33.3%)	547 (29.9%)	4,497 (36.8%)	1,252 (33.5%)	466 (32%)
South	4,373 (28.8%)	1,483 (31.8%)	652 (35.6%)	3,529 (28.9%)	1,181 (31.6%)	514 (35.3%)
West	1,765 (11.6%)	450 (9.7%)	217 (11.9%)	1,318 (10.8%)	338 (9%)	147 (10.1%)
Other	45 (0.3%)	23 (0.5%)	18 (1%)	27 (0.2%)	21 (0.6%)	11 (0.8%)
PLAN TYPE						
Comprehensive	6,132 (40.4%)	1,786 (38.3%)	687 (37.5%)	5,115 (41.9%)	1,458 (39%)	577 (39.6%)
EPO	36 (0.2%)	25 (0.5%)	7 (0.4%)	26 (0.2%)	19 (0.5%)	4 (0.3%)
HMO	1,683 (11.1%)	436 (9.4%)	200 (10.9%)	1,249 (10.2%)	346 (9.3%)	145 (9.9%)
POS	572 (3.8%)	171 (3.7%)	78 (4.3%)	461 (3.8%)	132 (3.5%)	60 (4.1%)
PPO	6,282 (41.4%)	2,025 (43.4%)	798 (43.6%)	5,026 (41.1%)	1,615 (43.2%)	631 (43.3%)
POS with Capitation	164 (1.1%)	77 (1.7%)	16 (0.9%)	132 (1.1%)	55 (1.5%)	14 (1%)
CDHP	115 (0.8%)	65 (1.4%)	21 (1.1%)	84 (0.7%)	53 (1.4%)	14 (1%)
HDHP	47 (0.3%)	29 (0.6%)	7 (0.4%)	33 (0.3%)	24 (0.6%)	5 (0.3%)
ELIXHAUSER INDEX						

	30 day			180 day		
Variable	**Clopidogrel N = 15,168**	**Ticagrelor N = 4,663**	**Prasugrel N = 1,830**	**Clopidogrel N = 12,218**	**Ticagrelor N = 3,740**	**Prasugrel N = 1,458**
Category 0	3,653 (24.1%)	1,280 (27.5%)	504 (27.5%)	3,025 (24.8%)	1,010 (27%)	412 (28.3%)
Category 1	3,004 (19.8%)	991 (21.3%)	425 (23.2%)	2,545 (20.8%)	828 (22.1%)	358 (24.6%)
Category 2	964 (6.4%)	338 (7.2%)	100 (5.5%)	765 (6.3%)	255 (6.8%)	81 (5.6%)
Category 3	3,557 (23.5%)	1,038 (22.3%)	467 (25.5%)	2,873 (23.5%)	848 (22.7%)	366 (25.1%)
Category 4	3,990 (26.3%)	1,016 (21.8%)	334 (18.3%)	3,010 (24.6%)	799 (21.4%)	241 (16.5%)
ACS TYPE						
STEMI	3,679 (24.3%)	1,507 (32.3%)	537 (29.3%)	2,968 (24.3%)	1,232 (32.9%)	432 (29.6%)
NSTEMI/UA	9,456 (62.3%)	2,585 (55.4%)	1,050 (57.4%)	7,671 (62.8%)	2,076 (55.5%)	841 (57.7%)
HIGH BLEEDING RISK						
High Bleeding Risk	8,258 (54.4%)	2,178 (46.7%)	859 (46.9%)	6,564 (53.7%)	1,737 (46.4%)	674 (46.2%)
MEDICATION HISTORY						
Anti-Diabetics						
Antidiabetics (Miscellaneous: *Biguanides, GLP-1 analogues DPP4, alpha-glucoside inhibitors, incretin mimetics, amylin analogues, glucagon, and combinations*)	2,854 (18.8%)	923 (19.8%)	372 (20.3%)	2,277 (18.6%)	752 (20.1%)	290 (19.9%)
Meglitinide	90 (0.6%)	26 (0.6%)	9 (0.5%)	73 (0.6%)	20 (0.5%)	8 (0.5%)
SGLT Inhibitors	115 (0.8%)	65 (1.4%)	15 (0.8%)	89 (0.7%)	45 (1.2%)	12 (0.8%)
Sulfnylureas	1,574 (10.4%)	450 (9.7%)	187 (10.2%)	1,261 (10.3%)	370 (9.9%)	146 (10%)
TZDs	202 (1.3%)	56 (1.2%)	35 (1.9%)	163 (1.3%)	48 (1.3%)	34 (2.3%)
Anti-hypertensive						
ACE Inhibitors	4,302 (28.4%)	1,226 (26.3%)	510 (27.9%)	3,452 (28.3%)	966 (25.8%)	418 (28.7%)
Beta Blockers	7,646 (50.4%)	2,038 (43.7%)	818 (44.7%)	6,125 (50.1%)	1,618 (43.3%)	653 (44.8%)
Calcium Channel Blockers	4,595 (30.3%)	1,310 (28.1%)	457 (25%)	3,689 (30.2%)	1,051 (28.1%)	364 (25%)

	30 day			180 day		
Variable	**Clopidogrel N = 15,168**	**Ticagrelor N = 4,663**	**Prasugrel N = 1,830**	**Clopidogrel N = 12,218**	**Ticagrelor N = 3,740**	**Prasugrel N = 1,458**
ARBs	3,748 (24.7%)	1,128 (24.2%)	426 (23.3%)	3,026 (24.8%)	916 (24.5%)	338 (23.2%)
Diuretics						
Loop Diuretics	2,545 (16.8%)	557 (11.9%)	195 (10.7%)	1,996 (16.3%)	442 (11.8%)	151 (10.4%)
Potassium Sparing Diuretics	893 (5.9%)	215 (4.6%)	95 (5.2%)	695 (5.7%)	181 (4.8%)	79 (5.4%)
Thiazide Diuretics	1,536 (10.1%)	455 (9.8%)	167 (9.1%)	1,234 (10.1%)	358 (9.6%)	135 (9.3%)
Other Medications						
Anti-Platelets	2,275 (15%)	693 (14.9%)	300 (16.4%)	1,814 (14.8%)	546 (14.6%)	229 (15.7%)
Anti-Arrhythmics	467 (3.1%)	84 (1.8%)	29 (1.6%)	348 (2.8%)	69 (1.8%)	20 (1.4%)
Anti-Hyperlipidimics	8,945 (59%)	2,634 (56.5%)	1,084 (59.2%)	7,182 (58.8%)	2,110 (56.4%)	871 (59.7%)
Anti-Depressants	2,914 (19.2%)	789 (16.9%)	318 (17.4%)	2,308 (18.9%)	631 (16.9%)	239 (16.4%)
Estrogens	344 (2.3%)	97 (2.1%)	33 (1.8%)	275 (2.3%)	84 (2.2%)	26 (1.8%)
PPIs	4,216 (27.8%)	1,156 (24.8%)	455 (24.9%)	3,382 (27.7%)	919 (24.6%)	356 (24.4%)
H2RAs	774 (5.1%)	232 (5%)	82 (4.5%)	614 (5%)	191 (5.1%)	68 (4.7%)

Acronyms: EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 4. 5 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users after Propensity Score Matching at 30 Days: MarketScan 2013-2018

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 Days			Clopidogrel : Prasugrel (1:1 PS Match) 30 Days			Ticagrelor : Prasugrel (1:1 PS Match) 30 Days		
Variable	**Clopidogrel N = 21,549**	**Ticagrelor N = 21,549**	**SDs**	**Clopidogrel N = 11,776**	**Prasugrel N = 11,776**	**SDs**	**Ticagrelor N = 11,263**	**Prasugrel N = 11,263**	**SDs**
AGE CATEGORY									
18-44 Years	1,470 (6.8%)	1,646 (7.6%)	-0.0310	925 (7.9%)	968 (8.2%)	-0.0110	866 (7.7%)	924 (8.2%)	-0.0185
45-64 Years	15,321 (71.1%)	15,255 (70.8%)	0.0066	8,980 (76.3%)	8,981 (76.3%)	0.0000	8,545 (75.9%)	8,548 (75.9%)	0.0000
65-84 Years	4,378 (20.3%)	4,293 (19.9%)	0.0100	1,825 (15.5%)	1,782 (15.1%)	0.0111	1,805 (16%)	1,747 (15.5%)	0.0137
85 Years & Above	380 (1.8%)	355 (1.6%)	0.0155	46 (0.4%)	45 (0.4%)	0.0000	47 (0.4%)	44 (0.4%)	0.0000
SEX									
Male	15,941 (74%)	15,930 (73.9%)	0.0023	9,233 (78.4%)	9,178 (77.9%)	0.0121	8,777 (77.9%)	8,755 (77.7%)	0.0048
Female	5,608 (26%)	5,619 (26.1%)	-0.0023	2,543 (21.6%)	2,598 (22.1%)	-0.0121	2,486 (22.1%)	2,508 (22.3%)	-0.0048
REGION									
Northeast	4,329 (20.1%)	4,404 (20.4%)	-0.0075	1,964 (16.7%)	1,908 (16.2%)	0.0135	1,840 (16.3%)	1,848 (16.4%)	-0.0027
North Central	5,697 (26.4%)	5,492 (25.5%)	0.0205	2,560 (21.7%)	2,529 (21.5%)	0.0049	2,487 (22.1%)	2,467 (21.9%)	0.0048
South	9,012 (41.8%)	9,167 (42.5%)	-0.0142	5,617 (47.7%)	5,669 (48.1%)	-0.0080	5,420 (48.1%)	5,377 (47.7%)	0.0080
West	2,375 (11%)	2,333 (10.8%)	0.0064	1,490 (12.7%)	1,505 (12.8%)	-0.0030	1,389 (12.3%)	1,416 (12.6%)	-0.0091
Other	136 (0.6%)	153 (0.7%)	-0.0124	145 (1.2%)	165 (1.4%)	-0.0177	127 (1.1%)	155 (1.4%)	-0.0270
PLAN TYPE									
Comprehensive	2,325 (10.8%)	2,250 (10.4%)	0.0130	1,235 (10.5%)	1,180 (10%)	0.0165	1,099 (9.8%)	1,143 (10.1%)	-0.0100
EPO	173 (0.8%)	199 (0.9%)	-0.0109	95 (0.8%)	107 (0.9%)	-0.0109	89 (0.8%)	102 (0.9%)	-0.0109
HMO	2,168 (10.1%)	2,155 (10%)	0.0033	1,158 (9.8%)	1,132 (9.6%)	0.0068	1,062 (9.4%)	1,068 (9.5%)	-0.0034
POS	1,381 (6.4%)	1,455 (6.8%)	-0.0161	725 (6.2%)	751 (6.4%)	-0.0082	701 (6.2%)	731 (6.5%)	-0.0123
PPO	11,989 (55.6%)	11,703 (54.3%)	0.0261	6,763 (57.4%)	6,794 (57.7%)	-0.0061	6,577 (58.4%)	6,462 (57.4%)	0.0203
POS with Capitation	242 (1.1%)	251 (1.2%)	-0.0094	71 (0.6%)	80 (0.7%)	-0.0124	75 (0.7%)	78 (0.7%)	0.0000
CDHP	2,020 (9.4%)	2,224 (10.3%)	-0.0302	1,080 (9.2%)	1,086 (9.2%)	0.0000	1,038 (9.2%)	1,053 (9.3%)	-0.0035
HDHP	1,251 (5.8%)	1,312 (6.1%)	-0.0127	649 (5.5%)	646 (5.5%)	0.0000	622 (5.5%)	626 (5.6%)	-0.0044
ELIXHAUSER INDEX									

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 Days			Clopidogrel : Prasugrel (1:1 PS Match) 30 Days			Ticagrelor : Prasugrel (1:1 PS Match) 30 Days		
Variable	**Clopidogrel N = 21,549**	**Ticagrelor N = 21,549**	**SDs**	**Clopidogrel N = 11,776**	**Prasugrel N = 11,776**	**SDs**	**Ticagrelor N = 11,263**	**Prasugrel N = 11,263**	**SDs**
Category 0	6,627 (30.8%)	6,781 (31.5%)	-0.0151	3,621 (30.7%)	3,612 (30.7%)	0.0000	3,543 (31.5%)	3,481 (30.9%)	0.0130
Category 1	5,770 (26.8%)	5,764 (26.7%)	0.0023	3,788 (32.2%)	3,669 (31.2%)	0.0215	3,445 (30.6%)	3,430 (30.5%)	0.0022
Category 2	1,600 (7.4%)	1,612 (7.5%)	-0.0038	693 (5.9%)	764 (6.5%)	-0.0249	721 (6.4%)	744 (6.6%)	-0.0081
Category 3	4,474 (20.8%)	4,375 (20.3%)	0.0124	2,438 (20.7%)	2,448 (20.8%)	-0.0025	2,308 (20.5%)	2,356 (20.9%)	-0.0099
Category 4	3,078 (14.3%)	3,017 (14%)	0.0086	1,236 (10.5%)	1,283 (10.9%)	-0.0129	1,246 (11.1%)	1,252 (11.1%)	0.0000
BLEEDING RISK									
High Bleeding Risk	8,448 (39.2%)	8,471 (39.3%)	-0.0020	4,150 (35.2%)	4,290 (36.4%)	-0.0250	4,083 (36.3%)	4,155 (36.9%)	-0.0125
MEDICATION HISTORY									
Anti-Diabetics									
Antidiabetics (Miscellaneous)	3,687 (17.1%)	3,779 (17.5%)	-0.0106	1,871 (15.9%)	2,029 (17.2%)	-0.0350	1,879 (16.7%)	1,949 (17.3%)	-0.0160
Meglitinide	62 (0.3%)	55 (0.3%)	0.0000	22 (0.2%)	27 (0.2%)	0.0000	20 (0.2%)	26 (0.2%)	0.0000
SGLT Inhibitors	469 (2.2%)	511 (2.4%)	-0.0133	182 (1.5%)	219 (1.9%)	-0.0309	210 (1.9%)	217 (1.9%)	0.0000
Sulfnylureas	1,501 (7%)	1,525 (7.1%)	-0.0039	741 (6.3%)	775 (6.6%)	-0.0122	736 (6.5%)	755 (6.7%)	-0.0081
TZDs	250 (1.2%)	245 (1.1%)	0.0094	124 (1.1%)	141 (1.2%)	-0.0094	132 (1.2%)	132 (1.2%)	0.0000
Anti-hypertensive									
ACE Inhibitors	4,837 (22.4%)	4,895 (22.7%)	-0.0072	2,548 (21.6%)	2,681 (22.8%)	-0.0289	2,468 (21.9%)	2,561 (22.7%)	-0.0192
Beta Blockers	6,421 (29.8%)	6,430 (29.8%)	0.0000	3,444 (29.2%)	3,546 (30.1%)	-0.0197	3,298 (29.3%)	3,376 (30%)	-0.0153
Calcium Channel Blockers	3,795 (17.6%)	3,928 (18.2%)	-0.0157	1,682 (14.3%)	1,871 (15.9%)	-0.0447	1,751 (15.5%)	1,815 (16.1%)	-0.0165
ARBs	3,738 (17.3%)	3,835 (17.8%)	-0.0131	1,927 (16.4%)	1,967 (16.7%)	-0.0081	1,862 (16.5%)	1,901 (16.9%)	-0.0107
Diuretics									
Loop Diuretics	1,241 (5.8%)	1,163 (5.4%)	0.0174	492 (4.2%)	559 (4.7%)	-0.0242	538 (4.8%)	530 (4.7%)	0.0047
Potassium Sparing Diuretics	630 (2.9%)	619 (2.9%)	0.0000	329 (2.8%)	338 (2.9%)	-0.0060	317 (2.8%)	317 (2.8%)	0.0000
Thiazide Diuretics	1,461 (6.8%)	1,503 (7%)	-0.0079	707 (6%)	777 (6.6%)	-0.0247	720 (6.4%)	748 (6.6%)	-0.0081
Other Medications									
Anti-Platelets	2,144 (9.9%)	2,085 (9.7%)	0.0067	1,227 (10.4%)	1,294 (11%)	-0.0194	1,186 (10.5%)	1,224 (10.9%)	-0.0129

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 Days			Clopidogrel : Prasugrel (1:1 PS Match) 30 Days			Ticagrelor : Prasugrel (1:1 PS Match) 30 Days		
Variable	**Clopidogrel N = 21,549**	**Ticagrelor N = 21,549**	**SDs**	**Clopidogrel N = 11,776**	**Prasugrel N = 11,776**	**SDs**	**Ticagrelor N = 11,263**	**Prasugrel N = 11,263**	**SDs**
Anti-Arrhythmics	176 (0.8%)	156 (0.7%)	0.0116	81 (0.7%)	89 (0.8%)	-0.0116	82 (0.7%)	81 (0.7%)	0.0000
Anti-Hyperlipidimics	9,164 (42.5%)	9,354 (43.4%)	-0.0182	5,044 (42.8%)	5,221 (44.3%)	-0.0303	4,844 (43%)	4,986 (44.3%)	-0.0262
Anti-Depressants	3,594 (16.7%)	3,680 (17.1%)	-0.0107	1,860 (15.8%)	1,942 (16.5%)	-0.0190	1,803 (16%)	1,881 (16.7%)	-0.0189
Estrogens	319 (1.5%)	348 (1.6%)	-0.0081	187 (1.6%)	204 (1.7%)	-0.0079	175 (1.6%)	196 (1.7%)	-0.0079
PPIs	3,951 (18.3%)	4,020 (18.7%)	-0.0103	2,045 (17.4%)	2,155 (18.3%)	-0.0235	1,963 (17.4%)	2,084 (18.5%)	-0.0287
H2RAs	594 (2.8%)	608 (2.8%)	0.0000	261 (2.2%)	266 (2.3%)	-0.0067	235 (2.1%)	259 (2.3%)	-0.0136

Acronyms: PS: propensity score, EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 4. 6 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users after Propensity Score Matching at 180 Days MarketScan: 2013-2018

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 Days			Clopidogrel : Prasugrel (1:1 PS Match) 180 Days			Ticagrelor : Prasugrel (1:1 PS Match) 180 Days		
Variable	**Clopidogrel N = 16,880**	**Ticagrelor N = 16,880**	**SDs**	**Clopidogrel N = 9,615**	**Prasugrel N = 9,615**	**SDs**	**Ticagrelor N = 9,130**	**Prasugrel N = 9,130**	**SDs**
AGE CATEGORY									
18-44 Years	1,155 (6.8%)	1,238 (7.3%)	-0.0195	752 (7.8%)	781 (8.1%)	-0.0111	701 (7.7%)	757 (8.3%)	-0.0221
45-64 Years	11,972 (70.9%)	11,965 (70.9%)	0.0000	7,391 (76.9%)	7,387 (76.8%)	0.0024	6,955 (76.2%)	6,948 (76.1%)	0.0023
65-84 Years	3,420 (20.3%)	3,386 (20.1%)	0.0050	1,437 (14.9%)	1,411 (14.7%)	0.0056	1,440 (15.8%)	1,392 (15.2%)	0.0166
85 Years & Above	333 (2%)	291 (1.7%)	0.0223	35 (0.4%)	36 (0.4%)	0.0000	34 (0.4%)	33 (0.4%)	0.0000
SEX									
Male	12,536 (74.3%)	12,516 (74.1%)	0.0046	7,594 (79%)	7,511 (78.1%)	0.0219	7,132 (78.1%)	7,110 (77.9%)	0.0048
Female	4,344 (25.7%)	4,364 (25.9%)	-0.0046	2,021 (21%)	2,104 (21.9%)	-0.0219	1,998 (21.9%)	2,020 (22.1%)	-0.0048
REGION									
Northeast	3,477 (20.6%)	3,459 (20.5%)	0.0025	1,625 (16.9%)	1,596 (16.6%)	0.0080	1,538 (16.8%)	1,536 (16.8%)	0.0000
North Central	4,520 (26.8%)	4,413 (26.1%)	0.0159	2,152 (22.4%)	2,120 (22%)	0.0096	2,070 (22.7%)	2,067 (22.6%)	0.0024
South	7,029 (41.6%)	7,140 (42.3%)	-0.0142	4,570 (47.5%)	4,637 (48.2%)	-0.0140	4,396 (48.1%)	4,340 (47.5%)	0.0120
West	1,758 (10.4%)	1,759 (10.4%)	0.0000	1,172 (12.2%)	1,157 (12%)	0.0061	1,038 (11.4%)	1,090 (11.9%)	-0.0156
Other	96 (0.6%)	109 (0.6%)	0.0000	96 (1%)	105 (1.1%)	-0.0098	88 (1%)	97 (1.1%)	-0.0098
PLAN TYPE									
Comprehensive	1,906 (11.3%)	1,820 (10.8%)	0.0159	1,043 (10.8%)	996 (10.4%)	0.0130	937 (10.3%)	955 (10.5%)	-0.0066
EPO	133 (0.8%)	143 (0.8%)	0.0000	78 (0.8%)	82 (0.9%)	-0.0109	70 (0.8%)	77 (0.8%)	0.0000
HMO	1,608 (9.5%)	1,648 (9.8%)	-0.0102	849 (8.8%)	880 (9.2%)	-0.0140	845 (9.3%)	853 (9.3%)	0.0000
POS	998 (5.9%)	1,066 (6.3%)	-0.0167	607 (6.3%)	609 (6.3%)	0.0000	576 (6.3%)	583 (6.4%)	-0.0041
PPO	9,414 (55.8%)	9,156 (54.2%)	0.0322	5,510 (57.3%)	5,539 (57.6%)	-0.0061	5,231 (57.3%)	5,194 (56.9%)	0.0081
POS with Capitation	189 (1.1%)	199 (1.2%)	-0.0094	55 (0.6%)	63 (0.7%)	-0.0124	66 (0.7%)	60 (0.7%)	0.0000
CDHP	1,682 (10%)	1,813 (10.7%)	-0.0230	977 (10.2%)	941 (9.8%)	0.0133	918 (10.1%)	924 (10.1%)	0.0000
HDHP	950 (5.6%)	1,035 (6.1%)	-0.0213	496 (5.2%)	505 (5.3%)	-0.0045	487 (5.3%)	484 (5.3%)	0.0000

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 Days			Clopidogrel : Prasugrel (1:1 PS Match) 180 Days			Ticagrelor : Prasugrel (1:1 PS Match) 180 Days		
Variable	**Clopidogrel N = 16,880**	**Ticagrelor N = 16,880**	**SDs**	**Clopidogrel N = 9,615**	**Prasugrel N = 9,615**	**SDs**	**Ticagrelor N = 9,130**	**Prasugrel N = 9,130**	**SDs**
ELIXHAUSER INDEX									
Category 0	5,255 (31.1%)	5,322 (31.5%)	-0.0086	3,005 (31.3%)	2,952 (30.7%)	0.0130	2,852 (31.2%)	2,807 (30.7%)	0.0108
Category 1	4,720 (28%)	4,641 (27.5%)	0.0112	3,166 (32.9%)	3,127 (32.5%)	0.0085	2,915 (31.9%)	2,894 (31.7%)	0.0043
Category 2	1,245 (7.4%)	1,258 (7.5%)	-0.0038	563 (5.9%)	603 (6.3%)	-0.0167	574 (6.3%)	584 (6.4%)	-0.0041
Category 3	3,394 (20.1%)	3,415 (20.2%)	-0.0025	1,920 (20%)	1,966 (20.4%)	-0.0100	1,830 (20%)	1,899 (20.8%)	-0.0199
Category 4	2,266 (13.4%)	2,244 (13.3%)	0.0029	961 (10%)	967 (10.1%)	-0.0033	959 (10.5%)	946 (10.4%)	0.0033
BLEEDING RISK									
High Bleeding Risk	6,448 (38.2%)	6,450 (38.2%)	0.0000	3,321 (34.5%)	3,427 (35.6%)	-0.0231	3,244 (35.5%)	3,319 (36.4%)	-0.0188
MEDICATION HISTORY									
Anti-Diabetics									
Antidiabetics (Miscellaneous)	2,811 (16.7%)	2,905 (17.2%)	-0.0133	1,510 (15.7%)	1,599 (16.6%)	-0.0245	1,457 (16%)	1,542 (16.9%)	-0.0243
Meglitinide	41 (0.2%)	40 (0.2%)	0.0000	19 (0.2%)	22 (0.2%)	0.0000	21 (0.2%)	21 (0.2%)	0.0000
SGLT inhibitors	358 (2.1%)	367 (2.2%)	-0.0069	141 (1.5%)	169 (1.8%)	-0.0236	163 (1.8%)	170 (1.9%)	-0.0074
Sulfnylureas	1,136 (6.7%)	1,161 (6.9%)	-0.0079	597 (6.2%)	612 (6.4%)	-0.0082	572 (6.3%)	592 (6.5%)	-0.0082
TZDs	191 (1.1%)	185 (1.1%)	0.0000	108 (1.1%)	113 (1.2%)	-0.0094	98 (1.1%)	115 (1.3%)	-0.0184
Anti-hypertensive									
ACE Inhibitors	3,699 (21.9%)	3,770 (22.3%)	-0.0096	2,128 (22.1%)	2,158 (22.4%)	-0.0072	1,971 (21.6%)	2,068 (22.7%)	-0.0265
Beta Blockers	5,015 (29.7%)	4,961 (29.4%)	0.0066	2,720 (28.3%)	2,839 (29.5%)	-0.0265	2,632 (28.8%)	2,699 (29.6%)	-0.0176
Calcium Channel Blockers	3,001 (17.8%)	3,037 (18%)	-0.0052	1,404 (14.6%)	1,474 (15.3%)	-0.0196	1,400 (15.3%)	1,432 (15.7%)	-0.0111
ARBs	2,929 (17.4%)	3,052 (18.1%)	-0.0183	1,449 (15.1%)	1,582 (16.5%)	-0.0384	1,469 (16.1%)	1,511 (16.5%)	-0.0108
Diuretics									
Loop Diuretics	903 (5.3%)	876 (5.2%)	0.0045	401 (4.2%)	439 (4.6%)	-0.0195	410 (4.5%)	418 (4.6%)	-0.0048
Potassium Sparing Diuretics	490 (2.9%)	476 (2.8%)	0.0060	274 (2.8%)	276 (2.9%)	-0.0060	256 (2.8%)	257 (2.8%)	0.0000
Thiazide Diuretics	1,093 (6.5%)	1,135 (6.7%)	-0.0081	581 (6%)	611 (6.4%)	-0.0166	538 (5.9%)	596 (6.5%)	-0.0249

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 Days			Clopidogrel : Prasugrel (1:1 PS Match) 180 Days			Ticagrelor : Prasugrel (1:1 PS Match) 180 Days		
Variable	**Clopidogrel N = 16,880**	**Ticagrelor N = 16,880**	**SDs**	**Clopidogrel N = 9,615**	**Prasugrel N = 9,615**	**SDs**	**Ticagrelor N = 9,130**	**Prasugrel N = 9,130**	**SDs**
Other Medications									
Anti-Platelets	1,622 (9.6%)	1,582 (9.4%)	0.0068	919 (9.6%)	981 (10.2%)	-0.0201	925 (10.1%)	923 (10.1%)	0.0000
Anti-Arrhythmics	123 (0.7%)	120 (0.7%)	0.0000	68 (0.7%)	67 (0.7%)	0.0000	63 (0.7%)	64 (0.7%)	0.0000
Anti-Hyperlipidimics	7,130 (42.2%)	7,228 (42.8%)	-0.0121	4,058 (42.2%)	4,206 (43.7%)	-0.0303	3,892 (42.6%)	3,993 (43.7%)	-0.0222
Anti-Depressants	2,782 (16.5%)	2,822 (16.7%)	-0.0054	1,526 (15.9%)	1,571 (16.3%)	-0.0109	1,441 (15.8%)	1,510 (16.5%)	-0.0190
Estrogens	266 (1.6%)	280 (1.7%)	-0.0079	151 (1.6%)	163 (1.7%)	-0.0079	153 (1.7%)	155 (1.7%)	0.0000
PPIs	3,118 (18.5%)	3,161 (18.7%)	-0.0051	1,652 (17.2%)	1,705 (17.7%)	-0.0132	1,555 (17%)	1,602 (17.5%)	-0.0132
H2RAs	484 (2.9%)	469 (2.8%)	0.0060	209 (2.2%)	215 (2.2%)	0.0000	214 (2.3%)	209 (2.3%)	0.0000

Acronyms: PS: propensity score, EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 4. 7 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users after Propensity Score Matching for the CCAE Sample Population at 30 Days (Sensitivity Analysis): MarketScan 2013-2018

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 days			Clopidogrel : Prasugrel (1:1 PS Match) 30 days			Ticagrelor : Prasugrel (1:1 PS Match) 30 days		
Variable	**Clopidogrel N = 16,828**	**Ticagrelor N = 16,828**	**SDs**	**Clopidogrel N = 9,951**	**Prasugrel N = 9,951**	**SDs**	**Ticagrelor N = 9,341**	**Prasugrel N = 9,341**	**SDs**
AGE CATEGORY									
18-45 Years	1,779 (10.6%)	1,981 (11.8%)	-0.0381	1,174 (11.8%)	1,171 (11.8%)	0.0000	1,079 (11.6%)	1,103 (11.8%)	-0.0062
46-55 Years	5,843 (34.7%)	5,939 (35.3%)	-0.0126	3,555 (35.7%)	3,580 (36%)	-0.0063	3,352 (35.9%)	3,380 (36.2%)	-0.0062
56-65 Years	9,206 (54.7%)	8,908 (52.9%)	0.0361	5,222 (52.5%)	5,200 (52.3%)	0.0040	4,910 (52.6%)	4,858 (52%)	0.0120
SEX									
Male	12,899 (76.7%)	12,934 (76.9%)	-0.0047	7,874 (79.1%)	7,855 (78.9%)	0.0049	7,375 (79%)	7,357 (78.8%)	0.0049
Female	3,929 (23.3%)	3,894 (23.1%)	0.0047	2,077 (20.9%)	2,096 (21.1%)	-0.0049	1,966 (21%)	1,984 (21.2%)	-0.0049
REGION									
Northeast	3,136 (18.6%)	3,154 (18.7%)	-0.0026	1,519 (15.3%)	1,513 (15.2%)	0.0028	1,466 (15.7%)	1,438 (15.4%)	0.0083
North Central	4,062 (24.1%)	4,023 (23.9%)	0.0047	2,051 (20.6%)	1,989 (20%)	0.0149	1,860 (19.9%)	1,906 (20.4%)	-0.0125
South	7,572 (45%)	7,622 (45.3%)	-0.0060	4,944 (49.7%)	5,012 (50.4%)	-0.0140	4,788 (51.3%)	4,673 (50%)	0.0260
West	1,951 (11.6%)	1,899 (11.3%)	0.0094	1,298 (13%)	1,290 (13%)	0.0000	1,121 (12%)	1,201 (12.9%)	-0.0273
Other	107 (0.6%)	130 (0.8%)	-0.0240	139 (1.4%)	147 (1.5%)	-0.0084	106 (1.1%)	123 (1.3%)	-0.0184
PLAN TYPE									
Comprehensive	517 (3.1%)	509 (3%)	0.0058	474 (4.8%)	490 (4.9%)	-0.0047	343 (3.7%)	417 (4.5%)	-0.0404
EPO	150 (0.9%)	165 (1%)	-0.0103	96 (1%)	100 (1%)	0.0000	91 (1%)	87 (0.9%)	0.0103
HMO	1,689 (10%)	1,676 (10%)	0.0000	899 (9%)	933 (9.4%)	-0.0138	846 (9.1%)	868 (9.3%)	-0.0069
POS	1,215 (7.2%)	1,240 (7.4%)	-0.0077	646 (6.5%)	673 (6.8%)	-0.0120	654 (7%)	651 (7%)	0.0000
PPO	9,890 (58.8%)	9,616 (57.1%)	0.0344	6,060 (60.9%)	5,991 (60.2%)	0.0143	5,709 (61.1%)	5,597 (59.9%)	0.0245
POS with Capitation	153 (0.9%)	167 (1%)	-0.0103	63 (0.6%)	64 (0.6%)	0.0000	61 (0.7%)	62 (0.7%)	0.0000
CDHP	1,964 (11.7%)	2,171 (12.9%)	-0.0365	1,046 (10.5%)	1,064 (10.7%)	-0.0065	1,029 (11%)	1,039 (11.1%)	-0.0032
HDHP	1,250 (7.4%)	1,284 (7.6%)	-0.0076	667 (6.7%)	636 (6.4%)	0.0121	608 (6.5%)	620 (6.6%)	-0.0040
ELIXHAUSER INDEX									
Category 0	5,387 (32%)	5,506 (32.7%)	-0.0150	3,120 (31.4%)	3,110 (31.3%)	0.0022	3,036 (32.5%)	2,925 (31.3%)	0.0257

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 days			Clopidogrel : Prasugrel (1:1 PS Match) 30 days			Ticagrelor : Prasugrel (1:1 PS Match) 30 days		
Variable	**Clopidogrel N = 16,828**	**Ticagrelor N = 16,828**	**SDs**	**Clopidogrel N = 9,951**	**Prasugrel N = 9,951**	**SDs**	**Ticagrelor N = 9,341**	**Prasugrel N = 9,341**	**SDs**
Category 1	4,773 (28.4%)	4,667 (27.7%)	0.0156	3,309 (33.3%)	3,239 (32.5%)	0.0170	3,015 (32.3%)	2,990 (32%)	0.0064
Category 2	1,251 (7.4%)	1,288 (7.7%)	-0.0114	634 (6.4%)	665 (6.7%)	-0.0121	594 (6.4%)	635 (6.8%)	-0.0161
Category 3	3,400 (20.2%)	3,380 (20.1%)	0.0025	1,969 (19.8%)	1,985 (19.9%)	-0.0025	1,805 (19.3%)	1,881 (20.1%)	-0.0201
Category 4	2,017 (12%)	1,987 (11.8%)	0.0062	919 (9.2%)	952 (9.6%)	-0.0137	891 (9.5%)	910 (9.7%)	-0.0068
BLEEDING RISK									
High Bleeding Risk	6,331 (37.6%)	6,200 (36.8%)	0.0166	3,319 (33.4%)	3,440 (34.6%)	-0.0253	3,154 (33.8%)	3,281 (35.1%)	-0.0274
MEDICATION HISTORY									
Anti-Diabetics									
Antidiabetics (Miscellaneous)	2,763 (16.4%)	2,828 (16.8%)	-0.0108	1,545 (15.5%)	1,653 (16.6%)	-0.0300	1,506 (16.1%)	1,585 (17%)	-0.0242
Meglitinide	28 (0.2%)	25 (0.1%)	0.0258	12 (0.1%)	18 (0.2%)	-0.0258	15 (0.2%)	17 (0.2%)	0.0000
SGLT inhibitors	397 (2.4%)	453 (2.7%)	-0.0190	194 (1.9%)	198 (2%)	-0.0072	186 (2%)	203 (2.2%)	-0.0139
Sulfnylureas	1,036 (6.2%)	1,057 (6.3%)	-0.0041	547 (5.5%)	592 (5.9%)	-0.0173	523 (5.6%)	564 (6%)	-0.0171
TZDs	156 (0.9%)	187 (1.1%)	-0.0201	103 (1%)	104 (1%)	0.0000	112 (1.2%)	105 (1.1%)	0.0094
Anti-Hypertensive									
ACE Inhibitors	3,625 (21.5%)	3,661 (21.8%)	-0.0073	2,099 (21.1%)	2,175 (21.9%)	-0.0195	1,965 (21%)	2,040 (21.8%)	-0.0195
Beta Blockers	4,515 (26.8%)	4,423 (26.3%)	0.0113	2,621 (26.3%)	2,730 (27.4%)	-0.0248	2,498 (26.7%)	2,571 (27.5%)	-0.0180
Calcium Channel Blockers	2,570 (15.3%)	2,624 (15.6%)	-0.0083	1,359 (13.7%)	1,419 (14.3%)	-0.0173	1,286 (13.8%)	1,352 (14.5%)	-0.0201
ARBs	2,609 (15.5%)	2,750 (16.3%)	-0.0219	1,456 (14.6%)	1,540 (15.5%)	-0.0252	1,425 (15.3%)	1,469 (15.7%)	-0.0111
Diuretics									
Loop Diuretics	618 (3.7%)	614 (3.6%)	0.0053	357 (3.6%)	365 (3.7%)	-0.0053	325 (3.5%)	335 (3.6%)	-0.0054
Potassium Sparing Diuretics	414 (2.5%)	415 (2.5%)	0.0000	241 (2.4%)	246 (2.5%)	-0.0065	213 (2.3%)	229 (2.5%)	-0.0131
Thiazide Diuretics	1,045 (6.2%)	1,040 (6.2%)	0.0000	577 (5.8%)	613 (6.2%)	-0.0168	569 (6.1%)	576 (6.2%)	-0.0042
Other Medications									
Anti-Platelets	1,479 (8.8%)	1,413 (8.4%)	0.0143	949 (9.5%)	988 (9.9%)	-0.0135	898 (9.6%)	910 (9.7%)	-0.0034
Anti-Arrhythmics	75 (0.4%)	73 (0.4%)	0.0000	50 (0.5%)	61 (0.6%)	-0.0135	49 (0.5%)	51 (0.5%)	0.0000

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 days			Clopidogrel : Prasugrel (1:1 PS Match) 30 days			Ticagrelor : Prasugrel (1:1 PS Match) 30 days		
Variable	**Clopidogrel N = 16,828**	**Ticagrelor N = 16,828**	**SDs**	**Clopidogrel N = 9,951**	**Prasugrel N = 9,951**	**SDs**	**Ticagrelor N = 9,341**	**Prasugrel N = 9,341**	**SDs**
Anti-Hyperlipidimics	6,686 (39.7%)	6,692 (39.8%)	-0.0020	3,994 (40.1%)	4,136 (41.6%)	-0.0305	3,738 (40%)	3,901 (41.8%)	-0.0366
Anti-Depressants	2,826 (16.8%)	2,860 (17%)	-0.0053	1,551 (15.6%)	1,630 (16.4%)	-0.0218	1,487 (15.9%)	1,540 (16.5%)	-0.0163
Estrogens	243 (1.4%)	246 (1.5%)	-0.0084	152 (1.5%)	171 (1.7%)	-0.0159	157 (1.7%)	160 (1.7%)	0.0000
PPIs	2,810 (16.7%)	2,888 (17.2%)	-0.0133	1,633 (16.4%)	1,700 (17.1%)	-0.0187	1,580 (16.9%)	1,617 (17.3%)	-0.0106
H2RAs	364 (2.2%)	380 (2.3%)	-0.0067	157 (1.6%)	185 (1.9%)	-0.0229	170 (1.8%)	176 (1.9%)	-0.0074

Acronyms: PS: propensity score, CCAE: Commercial Claims and Encounters, EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 4. 8 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users after Propensity Score Matching for the CCAE Sample Population at 30 days (Sensitivity Analysis) : MarketScan 2013-2018

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 days			Clopidogrel : Prasugrel (1:1 PS Match) 180 days			Ticagrelor : Prasugrel (1:1 PS Match) s180 days		
Variable	**Clopidogrel N = 13,103**	**Ticagrelor N = 13,103**	**SDs**	**Clopidogrel N = 8,156**	**Prasugrel N = 8,156**	**SDs**	**Ticagrelor N = 7,612**	**Prasugrel N = 7,612**	**SDs**
AGE CATEGORY									
18-45 Years	1,382 (10.5%)	1,490 (11.4%)	-0.0288	943 (11.6%)	955 (11.7%)	-0.0031	880 (11.6%)	891 (11.7%)	-0.0031
46-55 Years	4,679 (35.7%)	4,764 (36.4%)	-0.0146	3,005 (36.8%)	3,013 (36.9%)	-0.0021	2,812 (36.9%)	2,834 (37.2%)	-0.0062
56-65 Years	7,042 (53.7%)	6,849 (52.3%)	0.0281	4,208 (51.6%)	4,188 (51.3%)	0.0060	3,920 (51.5%)	3,887 (51.1%)	0.0080
SEX									
Male	10,042 (76.6%)	10,091 (77%)	-0.0095	6,482 (79.5%)	6,459 (79.2%)	0.0074	6,024 (79.1%)	6,016 (79%)	0.0025
Female	3,061 (23.4%)	3,012 (23%)	0.0095	1,674 (20.5%)	1,697 (20.8%)	-0.0074	1,588 (20.9%)	1,596 (21%)	-0.0025
REGION									
Northeast	2,517 (19.2%)	2,532 (19.3%)	-0.0025	1,300 (15.9%)	1,277 (15.7%)	0.0055	1,211 (15.9%)	1,220 (16%)	-0.0027
North Central	3,183 (24.3%)	3,157 (24.1%)	0.0047	1,678 (20.6%)	1,656 (20.3%)	0.0074	1,563 (20.5%)	1,573 (20.7%)	-0.0049
South	5,879 (44.9%)	5,894 (45%)	-0.0020	4,081 (50%)	4,118 (50.5%)	-0.0100	3,865 (50.8%)	3,778 (49.6%)	0.0240
West	1,443 (11%)	1,431 (10.9%)	0.0032	1,004 (12.3%)	1,011 (12.4%)	-0.0030	897 (11.8%)	958 (12.6%)	-0.0244
Other	81 (0.6%)	89 (0.7%)	-0.0124	93 (1.1%)	94 (1.2%)	-0.0094	76 (1%)	83 (1.1%)	-0.0098
PLAN TYPE									
Comprehensive	383 (2.9%)	380 (2.9%)	0.0000	412 (5.1%)	415 (5.1%)	0.0000	291 (3.8%)	333 (4.4%)	-0.0303
EPO	118 (0.9%)	117 (0.9%)	0.0000	79 (1%)	78 (1%)	0.0000	59 (0.8%)	72 (0.9%)	-0.0109
HMO	1,288 (9.8%)	1,325 (10.1%)	-0.0100	750 (9.2%)	736 (9%)	0.0070	688 (9%)	689 (9.1%)	-0.0035
POS	889 (6.8%)	910 (6.9%)	-0.0040	555 (6.8%)	549 (6.7%)	0.0040	504 (6.6%)	520 (6.8%)	-0.0080
PPO	7,787 (59.4%)	7,545 (57.6%)	0.0365	4,915 (60.3%)	4,905 (60.1%)	0.0041	4,620 (60.7%)	4,581 (60.2%)	0.0102
POS with Capitation	126 (1%)	135 (1%)	0.0000	43 (0.5%)	49 (0.6%)	-0.0135	48 (0.6%)	49 (0.6%)	0.0000
CDHP	1,572 (12%)	1,670 (12.7%)	-0.0213	908 (11.1%)	924 (11.3%)	-0.0063	909 (11.9%)	887 (11.7%)	0.0062
HDHP	940 (7.2%)	1,021 (7.8%)	-0.0228	494 (6.1%)	500 (6.1%)	0.0000	493 (6.5%)	481 (6.3%)	0.0082
ELIXHAUSER INDEX									

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 days			Clopidogrel : Prasugrel (1:1 PS Match) 180 days			Ticagrelor : Prasugrel (1:1 PS Match) s180 days		
Variable	**Clopidogrel N = 13,103**	**Ticagrelor N = 13,103**	**SDs**	**Clopidogrel N = 8,156**	**Prasugrel N = 8,156**	**SDs**	**Ticagrelor N = 7,612**	**Prasugrel N = 7,612**	**SDs**
Category 0	4,221 (32.2%)	4,326 (33%)	-0.0171	2,567 (31.5%)	2,542 (31.2%)	0.0065	2,429 (31.9%)	2,387 (31.4%)	0.0108
Category 1	3,839 (29.3%)	3,855 (29.4%)	-0.0022	2,773 (34%)	2,765 (33.9%)	0.0021	2,526 (33.2%)	2,527 (33.2%)	0.0000
Category 2	968 (7.4%)	969 (7.4%)	0.0000	482 (5.9%)	520 (6.4%)	-0.0208	495 (6.5%)	494 (6.5%)	0.0000
Category 3	2,574 (19.6%)	2,516 (19.2%)	0.0101	1,620 (19.9%)	1,603 (19.7%)	0.0050	1,460 (19.2%)	1,510 (19.8%)	-0.0151
Category 4	1,501 (11.5%)	1,437 (11%)	0.0158	714 (8.8%)	726 (8.9%)	-0.0035	702 (9.2%)	694 (9.1%)	0.0035
BLEEDING RISK									
High Bleeding Risk	4,755 (36.3%)	4,661 (35.6%)	0.0146	2,708 (33.2%)	2,752 (33.7%)	-0.0106	2,549 (33.5%)	2,609 (34.3%)	-0.0169
MEDICATION HISTORY									
Anti-Diabetics									
Antidiabetics (Miscellaneous)	2,062 (15.7%)	2,142 (16.3%)	-0.0164	1,251 (15.3%)	1,305 (16%)	-0.0193	1,181 (15.5%)	1,230 (16.2%)	-0.0192
Meglitinide	24 (0.2%)	21 (0.2%)	0.0000	14 (0.2%)	14 (0.2%)	0.0000	11 (0.1%)	13 (0.2%)	-0.0258
SGLT Inhibitors	297 (2.3%)	320 (2.4%)	-0.0066	158 (1.9%)	153 (1.9%)	0.0000	151 (2%)	155 (2%)	0.0000
Sulfnylureas	765 (5.8%)	796 (6.1%)	-0.0127	446 (5.5%)	466 (5.7%)	-0.0087	425 (5.6%)	440 (5.8%)	-0.0086
TZDs	122 (0.9%)	138 (1.1%)	-0.0201	74 (0.9%)	79 (1%)	-0.0103	83 (1.1%)	77 (1%)	0.0098
Anti-hypertensive									
ACE Inhibitors	2,765 (21.1%)	2,767 (21.1%)	0.0000	1,689 (20.7%)	1,745 (21.4%)	-0.0172	1,627 (21.4%)	1,623 (21.3%)	0.0024
Beta Blockers	3,439 (26.2%)	3,334 (25.4%)	0.0183	2,037 (25%)	2,184 (26.8%)	-0.0411	1,932 (25.4%)	2,049 (26.9%)	-0.0341
Calcium Channel Blockers	1,988 (15.2%)	2,002 (15.3%)	-0.0028	1,063 (13%)	1,110 (13.6%)	-0.0177	996 (13.1%)	1,053 (13.8%)	-0.0205
ARBs	2,034 (15.5%)	2,095 (16%)	-0.0137	1,145 (14%)	1,240 (15.2%)	-0.0340	1,105 (14.5%)	1,182 (15.5%)	-0.0280
Diuretics									
Loop Diuretics	471 (3.6%)	442 (3.4%)	0.0109	261 (3.2%)	289 (3.5%)	-0.0167	258 (3.4%)	264 (3.5%)	-0.0055
Potassium Sparing Diuretics	324 (2.5%)	299 (2.3%)	0.0131	183 (2.2%)	199 (2.4%)	-0.0133	167 (2.2%)	179 (2.4%)	-0.0133
Thiazide Diuretics	761 (5.8%)	773 (5.9%)	-0.0043	462 (5.7%)	478 (5.9%)	-0.0086	407 (5.3%)	445 (5.8%)	-0.0218
Other Medications									
Anti-Platelets	1,069 (8.2%)	1,037 (7.9%)	0.0110	685 (8.4%)	748 (9.2%)	-0.0282	676 (8.9%)	695 (9.1%)	-0.0070

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 days			Clopidogrel : Prasugrel (1:1 PS Match) 180 days			Ticagrelor : Prasugrel (1:1 PS Match) s180 days		
Variable	**Clopidogrel N = 13,103**	**Ticagrelor N = 13,103**	**SDs**	**Clopidogrel N = 8,156**	**Prasugrel N = 8,156**	**SDs**	**Ticagrelor N = 7,612**	**Prasugrel N = 7,612**	**SDs**
Anti-Arrhythmics	43 (0.3%)	51 (0.4%)	-0.0169	46 (0.6%)	47 (0.6%)	0.0000	39 (0.5%)	42 (0.6%)	-0.0135
Anti-Hyperlipidimics	5,014 (38.3%)	5,067 (38.7%)	-0.0082	3,197 (39.2%)	3,332 (40.9%)	-0.0347	3,007 (39.5%)	3,121 (41%)	-0.0306
Anti-Depressants	2,162 (16.5%)	2,176 (16.6%)	-0.0027	1,257 (15.4%)	1,332 (16.3%)	-0.0246	1,228 (16.1%)	1,251 (16.4%)	-0.0081
Estrogens	200 (1.5%)	193 (1.5%)	0.0000	132 (1.6%)	137 (1.7%)	-0.0079	117 (1.5%)	122 (1.6%)	-0.0081
PPIs	2,185 (16.7%)	2,199 (16.8%)	-0.0027	1,296 (15.9%)	1,346 (16.5%)	-0.0163	1,213 (15.9%)	1,259 (16.5%)	-0.0163
H2RAs	278 (2.1%)	277 (2.1%)	0.0000	130 (1.6%)	147 (1.8%)	-0.0155	129 (1.7%)	139 (1.8%)	-0.0076

Acronyms: PS: propensity score, CCAE: Commercial Claims and Encounters EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 4. 9 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users after Propensity Score Matching for the MDCR Sample Population at 30 Days (Sensitivity Analysis): MarketScan 2013-2018

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 days			Clopidogrel : Prasugrel (1:1 PS Match) 30 days			Ticagrelor : Prasugrel (1:1 PS Match) 30 days		
Variable	**Clopidogrel N = 4,572**	**Ticagrelor N = 4,572**	**SDs**	**Clopidogrel N = 1,809**	**Prasugrel N = 1,809**	**SDs**	**Ticagrelor N = 1,747**	**Prasugrel N = 1,747**	**SDs**
AGE CATEGORY									
65-74 Years	2,637 (57.7%)	2,594 (56.7%)	0.0202	1,395 (77.1%)	1,407 (77.8%)	-0.0168	1,343 (76.9%)	1,347 (77.1%)	-0.0048
75-84 Years	1,574 (34.4%)	1,622 (35.5%)	-0.0231	367 (20.3%)	357 (19.7%)	0.0150	356 (20.4%)	355 (20.3%)	0.0025
85 Years & Above	361 (7.9%)	356 (7.8%)	0.0037	47 (2.6%)	45 (2.5%)	0.0063	48 (2.7%)	45 (2.6%)	0.0062
SEX									
Male	2,928 (64%)	2,900 (63.4%)	0.0125	1,317 (72.8%)	1,306 (72.2%)	0.0134	1,254 (71.8%)	1,251 (71.6%)	0.0044
Female	1,644 (36%)	1,672 (36.6%)	-0.0125	492 (27.2%)	503 (27.8%)	-0.0134	493 (28.2%)	496 (28.4%)	-0.0044
REGION									
Northeast	1,124 (24.6%)	1,123 (24.6%)	0.0000	357 (19.7%)	395 (21.8%)	-0.0518	356 (20.4%)	387 (22.2%)	-0.0440
North Central	1,518 (33.2%)	1,537 (33.6%)	-0.0085	552 (30.5%)	542 (30%)	0.0109	547 (31.3%)	533 (30.5%)	0.0173
South	1,459 (31.9%)	1,443 (31.6%)	0.0064	652 (36%)	642 (35.5%)	0.0104	631 (36.1%)	608 (34.8%)	0.0272
West	456 (10%)	446 (9.8%)	0.0067	235 (13%)	215 (11.9%)	0.0333	197 (11.3%)	201 (11.5%)	-0.0063
Other	15 (0.3%)	23 (0.5%)	-0.0317	13 (0.7%)	15 (0.8%)	-0.0116	16 (0.9%)	18 (1%)	-0.0103
PLAN TYPE									
Comprehensive	1,789 (39.1%)	1,783 (39%)	0.0020	678 (37.5%)	685 (37.9%)	-0.0083	680 (38.9%)	662 (37.9%)	0.0206
EPO	19 (0.4%)	20 (0.4%)	0.0000	10 (0.6%)	7 (0.4%)	0.0284	7 (0.4%)	7 (0.4%)	0.0000
HMO	443 (9.7%)	435 (9.5%)	0.0068	213 (11.8%)	200 (11.1%)	0.0220	182 (10.4%)	186 (10.6%)	-0.0065
POS	170 (3.7%)	171 (3.7%)	0.0000	94 (5.2%)	78 (4.3%)	0.0423	80 (4.6%)	77 (4.4%)	0.0096
PPO	1,999 (43.7%)	2,001 (43.8%)	-0.0020	771 (42.6%)	795 (43.9%)	-0.0262	754 (43.2%)	771 (44.1%)	-0.0181
POS with Capitation	71 (1.6%)	76 (1.7%)	-0.0079	13 (0.7%)	16 (0.9%)	-0.0225	16 (0.9%)	16 (0.9%)	0.0000
CDHP	52 (1.1%)	58 (1.3%)	-0.0184	22 (1.2%)	21 (1.2%)	0.0000	19 (1.1%)	21 (1.2%)	-0.0094
HDHP	29 (0.6%)	28 (0.6%)	0.0000	8 (0.4%)	7 (0.4%)	0.0000	9 (0.5%)	7 (0.4%)	0.0149
ELIXHAUSER INDEX									

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 days			Clopidogrel : Prasugrel (1:1 PS Match) 30 days			Ticagrelor : Prasugrel (1:1 PS Match) 30 days		
Variable	**Clopidogrel N = 4,572**	**Ticagrelor N = 4,572**	**SDs**	**Clopidogrel N = 1,809**	**Prasugrel N = 1,809**	**SDs**	**Ticagrelor N = 1,747**	**Prasugrel N = 1,747**	**SDs**
Category 0	1,281 (28%)	1,255 (27.4%)	0.0134	492 (27.2%)	499 (27.6%)	-0.0090	479 (27.4%)	493 (28.2%)	-0.0179
Category 1	951 (20.8%)	957 (20.9%)	-0.0025	444 (24.5%)	420 (23.2%)	0.0305	395 (22.6%)	403 (23.1%)	-0.0119
Category 2	314 (6.9%)	328 (7.2%)	-0.0117	102 (5.6%)	100 (5.5%)	0.0044	107 (6.1%)	98 (5.6%)	0.0213
Category 3	1,004 (22%)	1,026 (22.4%)	-0.0096	441 (24.4%)	458 (25.3%)	-0.0208	430 (24.6%)	431 (24.7%)	-0.0023
Category 4	1,022 (22.4%)	1,006 (22%)	0.0096	330 (18.2%)	332 (18.4%)	-0.0052	336 (19.2%)	322 (18.4%)	0.0205
HIGH BLEEDING RISK									
High Bleeding Risk	2,131 (46.6%)	2,153 (47.1%)	-0.0100	806 (44.6%)	847 (46.8%)	-0.0442	811 (46.4%)	802 (45.9%)	0.0100
MEDICATION HISTORY									
Anti-Diabetics									
Antidiabetics (Miscellaneous)	851 (18.6%)	909 (19.9%)	-0.0330	322 (17.8%)	367 (20.3%)	-0.0637	339 (19.4%)	348 (19.9%)	-0.0126
Meglitinide	20 (0.4%)	26 (0.6%)	-0.0284	4 (0.2%)	9 (0.5%)	-0.0508	9 (0.5%)	8 (0.5%)	0.0000
SGLT Inhibitors	62 (1.4%)	62 (1.4%)	0.0000	11 (0.6%)	15 (0.8%)	-0.0240	15 (0.9%)	15 (0.9%)	0.0000
Sulfnylureas	432 (9.4%)	443 (9.7%)	-0.0102	162 (9%)	182 (10.1%)	-0.0374	168 (9.6%)	172 (9.8%)	-0.0068
TZDs	57 (1.2%)	56 (1.2%)	0.0000	31 (1.7%)	35 (1.9%)	-0.0150	24 (1.4%)	28 (1.6%)	-0.0165
Anti-Hypertensive									
ACE Inhibitors	1,200 (26.2%)	1,204 (26.3%)	-0.0023	506 (28%)	505 (27.9%)	0.0022	477 (27.3%)	482 (27.6%)	-0.0067
Beta Blockers	2,003 (43.8%)	2,003 (43.8%)	0.0000	789 (43.6%)	814 (45%)	-0.0282	777 (44.5%)	777 (44.5%)	0.0000
Calcium Channel Blockers	1,293 (28.3%)	1,285 (28.1%)	0.0044	458 (25.3%)	452 (25%)	0.0069	433 (24.8%)	440 (25.2%)	-0.0092
ARBs	1,085 (23.7%)	1,109 (24.3%)	-0.0140	420 (23.2%)	419 (23.2%)	0.0000	420 (24%)	405 (23.2%)	0.0188
Diuretics									
Loop Diuretics	541 (11.8%)	548 (12%)	-0.0062	202 (11.2%)	194 (10.7%)	0.0160	193 (11%)	188 (10.8%)	0.0064
Potassium Sparing Diuretics	215 (4.7%)	211 (4.6%)	0.0047	88 (4.9%)	92 (5.1%)	-0.0092	81 (4.6%)	87 (5%)	-0.0187
Thiazide Diuretics	434 (9.5%)	445 (9.7%)	-0.0068	152 (8.4%)	165 (9.1%)	-0.0248	157 (9%)	156 (8.9%)	0.0035
Other Medications									

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 days			Clopidogrel : Prasugrel (1:1 PS Match) 30 days			Ticagrelor : Prasugrel (1:1 PS Match) 30 days		
Variable	**Clopidogrel N = 4,572**	**Ticagrelor N = 4,572**	**SDs**	**Clopidogrel N = 1,809**	**Prasugrel N = 1,809**	**SDs**	**Ticagrelor N = 1,747**	**Prasugrel N = 1,747**	**SDs**
Anti-Platelets	659 (14.4%)	687 (15%)	-0.0169	309 (17.1%)	298 (16.5%)	0.0160	276 (15.8%)	288 (16.5%)	-0.0190
Anti-Arrhythmics	91 (2%)	82 (1.8%)	0.0146	15 (0.8%)	28 (1.5%)	-0.0657	30 (1.7%)	27 (1.5%)	0.0159
Anti-Hyperlipidimics	2,588 (56.6%)	2,592 (56.7%)	-0.0020	1,051 (58.1%)	1,071 (59.2%)	-0.0223	1,001 (57.3%)	1,025 (58.7%)	-0.0284
Anti-Depressants	775 (17%)	781 (17.1%)	-0.0027	312 (17.2%)	312 (17.2%)	0.0000	292 (16.7%)	298 (17.1%)	-0.0107
Estrogens	97 (2.1%)	93 (2%)	0.0071	23 (1.3%)	33 (1.8%)	-0.0405	32 (1.8%)	32 (1.8%)	0.0000
PPIs	1,153 (25.2%)	1,134 (24.8%)	0.0092	437 (24.2%)	453 (25%)	-0.0186	438 (25.1%)	432 (24.7%)	0.0093
H2RAs	226 (4.9%)	230 (5%)	-0.0046	71 (3.9%)	82 (4.5%)	-0.0299	77 (4.4%)	81 (4.6%)	-0.0096

Acronyms: PS: propensity score, MDCR: Medicare Supplemental and Coordination of Benefits, EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 4. 10 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users after Propensity Score Matching for the MDCR Sample Population at 180 Days (Sensitivity Analysis): MarketScan 2013-2018

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 days			Clopidogrel : Prasugrel (1:1 PS Match) 180 days			Ticagrelor : Prasugrel (1:1 PS Match) 180 days		
Variable	**Clopidogrel N = 3,649**	**Ticagrelor N = 3,649**	**SDs**	**Clopidogrel N = 1,442**	**Prasugrel N = 1,442**	**SDs**	**Ticagrelor N = 1,388**	**Prasugrel N = 1,388**	**SDs**
AGE CATEGORY									
65-74 Years	2,070 (56.7%)	2,044 (56%)	0.0141	1,106 (76.7%)	1,114 (77.3%)	-0.0143	1,047 (75.4%)	1,064 (76.7%)	-0.0305
75-84 Years	1,295 (35.5%)	1,309 (35.9%)	-0.0083	296 (20.5%)	292 (20.2%)	0.0075	303 (21.8%)	288 (20.7%)	0.0269
85 Years & Above	284 (7.8%)	296 (8.1%)	-0.0111	40 (2.8%)	36 (2.5%)	0.0187	38 (2.7%)	36 (2.6%)	0.0062
SEX									
Male	2,283 (62.6%)	2,310 (63.3%)	-0.0145	1,041 (72.2%)	1,038 (72%)	0.0045	999 (72%)	986 (71%)	0.0222
Female	1,366 (37.4%)	1,339 (36.7%)	0.0145	401 (27.8%)	404 (28%)	-0.0045	389 (28%)	402 (29%)	-0.0222
REGION									
Northeast	948 (26%)	921 (25.2%)	0.0183	332 (23%)	319 (22.1%)	0.0215	303 (21.8%)	314 (22.6%)	-0.0193
North Central	1,201 (32.9%)	1,235 (33.8%)	-0.0191	451 (31.3%)	464 (32.2%)	-0.0193	456 (32.9%)	456 (32.9%)	0.0000
South	1,183 (32.4%)	1,146 (31.4%)	0.0215	512 (35.5%)	506 (35.1%)	0.0084	465 (33.5%)	472 (34%)	-0.0106
West	307 (8.4%)	333 (9.1%)	-0.0248	141 (9.8%)	145 (10.1%)	-0.0100	150 (10.8%)	135 (9.7%)	0.0363
Other	10 (0.3%)	14 (0.4%)	-0.0169	6 (0.4%)	8 (0.6%)	-0.0284	14 (1%)	11 (0.8%)	0.0212
PLAN TYPE									
Comprehensive	1,455 (39.9%)	1,455 (39.9%)	0.0000	561 (38.9%)	573 (39.7%)	-0.0164	550 (39.6%)	554 (39.9%)	-0.0061
EPO	10 (0.3%)	14 (0.4%)	-0.0169	3 (0.2%)	4 (0.3%)	-0.0200	5 (0.4%)	4 (0.3%)	0.0169
HMO	339 (9.3%)	344 (9.4%)	-0.0034	143 (9.9%)	145 (10.1%)	-0.0067	128 (9.2%)	137 (9.9%)	-0.0238
POS	135 (3.7%)	132 (3.6%)	0.0053	66 (4.6%)	60 (4.2%)	0.0195	56 (4%)	58 (4.2%)	-0.0101
PPO	1,597 (43.8%)	1,592 (43.6%)	0.0040	643 (44.6%)	627 (43.5%)	0.0222	622 (44.8%)	603 (43.4%)	0.0282
POS with Capitation	61 (1.7%)	54 (1.5%)	0.0159	12 (0.8%)	14 (1%)	-0.0212	10 (0.7%)	13 (0.9%)	-0.0225
CDHP	38 (1%)	41 (1.1%)	-0.0098	13 (0.9%)	14 (1%)	-0.0103	15 (1.1%)	14 (1%)	0.0098
HDHP	14 (0.4%)	17 (0.5%)	-0.0149	1 (0.1%)	5 (0.3%)	-0.0448	2 (0.1%)	5 (0.4%)	-0.0601
ELIXHAUSER INDEX									
Category 0	981 (26.9%)	994 (27.2%)	-0.0068	430 (29.8%)	407 (28.2%)	0.0353	380 (27.4%)	399 (28.7%)	-0.0289

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 days			Clopidogrel : Prasugrel (1:1 PS Match) 180 days			Ticagrelor : Prasugrel (1:1 PS Match) 180 days		
Variable	**Clopidogrel N = 3,649**	**Ticagrelor N = 3,649**	**SDs**	**Clopidogrel N = 1,442**	**Prasugrel N = 1,442**	**SDs**	**Ticagrelor N = 1,388**	**Prasugrel N = 1,388**	**SDs**
Category 1	806 (22.1%)	794 (21.8%)	0.0072	355 (24.6%)	354 (24.5%)	0.0023	343 (24.7%)	334 (24.1%)	0.0140
Category 2	231 (6.3%)	245 (6.7%)	-0.0162	79 (5.5%)	81 (5.6%)	-0.0044	74 (5.3%)	80 (5.8%)	-0.0218
Category 3	849 (23.3%)	832 (22.8%)	0.0119	352 (24.4%)	359 (24.9%)	-0.0116	350 (25.2%)	338 (24.4%)	0.0185
Category 4	782 (21.4%)	784 (21.5%)	-0.0024	226 (15.7%)	241 (16.7%)	-0.0271	241 (17.4%)	237 (17.1%)	0.0079
BLEEDING RISK									
High Bleeding Risk	1,719 (47.1%)	1,705 (46.7%)	0.0080	628 (43.6%)	668 (46.3%)	-0.0543	632 (45.5%)	640 (46.1%)	-0.0120
MEDICATION HISTORY									
Anti-Diabetics									
Antidiabetics (Miscellaneous)	717 (19.6%)	731 (20%)	-0.0100	236 (16.4%)	286 (19.8%)	-0.0884	266 (19.2%)	274 (19.7%)	-0.0126
Meglitinide	25 (0.7%)	20 (0.5%)	0.0259	7 (0.5%)	8 (0.6%)	-0.0135	6 (0.4%)	7 (0.5%)	-0.0149
SGLT inhibitors	41 (1.1%)	44 (1.2%)	-0.0094	13 (0.9%)	11 (0.8%)	0.0109	11 (0.8%)	12 (0.9%)	-0.0109
Sulfnylureas	379 (10.4%)	362 (9.9%)	0.0166	121 (8.4%)	141 (9.8%)	-0.0487	122 (8.8%)	134 (9.7%)	-0.0311
TZDs	44 (1.2%)	48 (1.3%)	-0.0090	29 (2%)	30 (2.1%)	-0.0071	21 (1.5%)	26 (1.9%)	-0.0309
Anti-Hypertensive									
ACE Inhibitors	932 (25.5%)	945 (25.9%)	-0.0092	372 (25.8%)	415 (28.8%)	-0.0674	393 (28.3%)	389 (28%)	0.0067
Beta Blockers	1,619 (44.4%)	1,584 (43.4%)	0.0202	639 (44.3%)	650 (45.1%)	-0.0161	607 (43.7%)	614 (44.2%)	-0.0101
Calcium Channel Blockers	1,013 (27.8%)	1,024 (28.1%)	-0.0067	351 (24.3%)	359 (24.9%)	-0.0139	353 (25.4%)	346 (24.9%)	0.0115
ARBs	893 (24.5%)	894 (24.5%)	0.0000	320 (22.2%)	334 (23.2%)	-0.0239	336 (24.2%)	321 (23.1%)	0.0259
Diuretics									
Loop Diuretics	443 (12.1%)	432 (11.8%)	0.0092	144 (10%)	150 (10.4%)	-0.0132	139 (10%)	136 (9.8%)	0.0067
Potassium Sparing Diuretics	179 (4.9%)	178 (4.9%)	0.0000	74 (5.1%)	76 (5.3%)	-0.0090	71 (5.1%)	71 (5.1%)	0.0000
Thiazide Diuretics	346 (9.5%)	349 (9.6%)	-0.0034	119 (8.3%)	133 (9.2%)	-0.0319	135 (9.7%)	126 (9.1%)	0.0206
Other Medications									
Anti-Platelets	547 (15%)	538 (14.7%)	0.0084	234 (16.2%)	227 (15.7%)	0.0137	217 (15.6%)	213 (15.3%)	0.0083
Anti-Arrhythmics	63 (1.7%)	67 (1.8%)	-0.0076	17 (1.2%)	20 (1.4%)	-0.0177	13 (0.9%)	19 (1.4%)	-0.0469

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 days			Clopidogrel : Prasugrel (1:1 PS Match) 180 days			Ticagrelor : Prasugrel (1:1 PS Match) 180 days		
Variable	**Clopidogrel N = 3,649**	**Ticagrelor N = 3,649**	**SDs**	**Clopidogrel N = 1,442**	**Prasugrel N = 1,442**	**SDs**	**Ticagrelor N = 1,388**	**Prasugrel N = 1,388**	**SDs**
Anti-Hyperlipidimics	2,075 (56.9%)	2,064 (56.6%)	0.0061	840 (58.3%)	860 (59.6%)	-0.0264	809 (58.3%)	810 (58.4%)	-0.0020
Anti-Depressants	624 (17.1%)	623 (17.1%)	0.0000	225 (15.6%)	236 (16.4%)	-0.0218	221 (15.9%)	227 (16.4%)	-0.0136
Estrogens	93 (2.5%)	80 (2.2%)	0.0198	33 (2.3%)	26 (1.8%)	0.0353	31 (2.2%)	25 (1.8%)	0.0286
PPIs	891 (24.4%)	896 (24.6%)	-0.0047	315 (21.8%)	355 (24.6%)	-0.0664	344 (24.8%)	335 (24.1%)	0.0163
H2RAs	172 (4.7%)	189 (5.2%)	-0.0231	67 (4.6%)	68 (4.7%)	-0.0047	64 (4.6%)	67 (4.8%)	-0.0095

Acronyms: PS: propensity score, MDCR: Medicare Supplemental and Coordination of Benefits, EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 4. 11 Comparative Risk of Secondary Effectiveness Outcomes after Propensity Score Matching

Ticagrelor vs Clopidogrel (HR (95%CI))	Prasugrel vs Clopidogrel (HR (95%CI))	Prasugrel vs Ticagrelor (HR (95%CI))
Stroke Events		
30 Days		
0.59 (0.30 1.17)	1.00 (0.35 2.85)	1.00 (0.35 2.85)
180 Days		
0.73 (0.48 1.11)	0.80 (0.44 1.44)	1.00 (0.53 1.89)
Coronary Artery Disease Events		
30 Days		
1.01 (0.88 1.15)	1.00 (0.81 1.22)	0.86 (0.71 1.05)
180 Days		
1.04 (0.94 1.16)	0.99 (0.85 1.15)	0.90 (0.78 1.05)
Heart Failure Events		
30 Days		
1.03 (0.85 1.25)	1.00 (0.75 1.33)	0.93 (0.70 1.23)
180 Days		
0.97 (0.85 1.10)	0.92 (0.76 1.10)	0.90 (0.78 1.05)
Peripheral Artery Disease Events		
30 Days		
0.60 (0.26 1.37)	0.22 (0.05 1.03)	2.00 (0.18 22.05)
180 Days		
0.84 (0.53 1.35)	0.58 (0.28 1.22)	0.67 (0.30 1.48)

Acronyms: (HR (95%CI)): hazard ratio and its 95% confidence interval

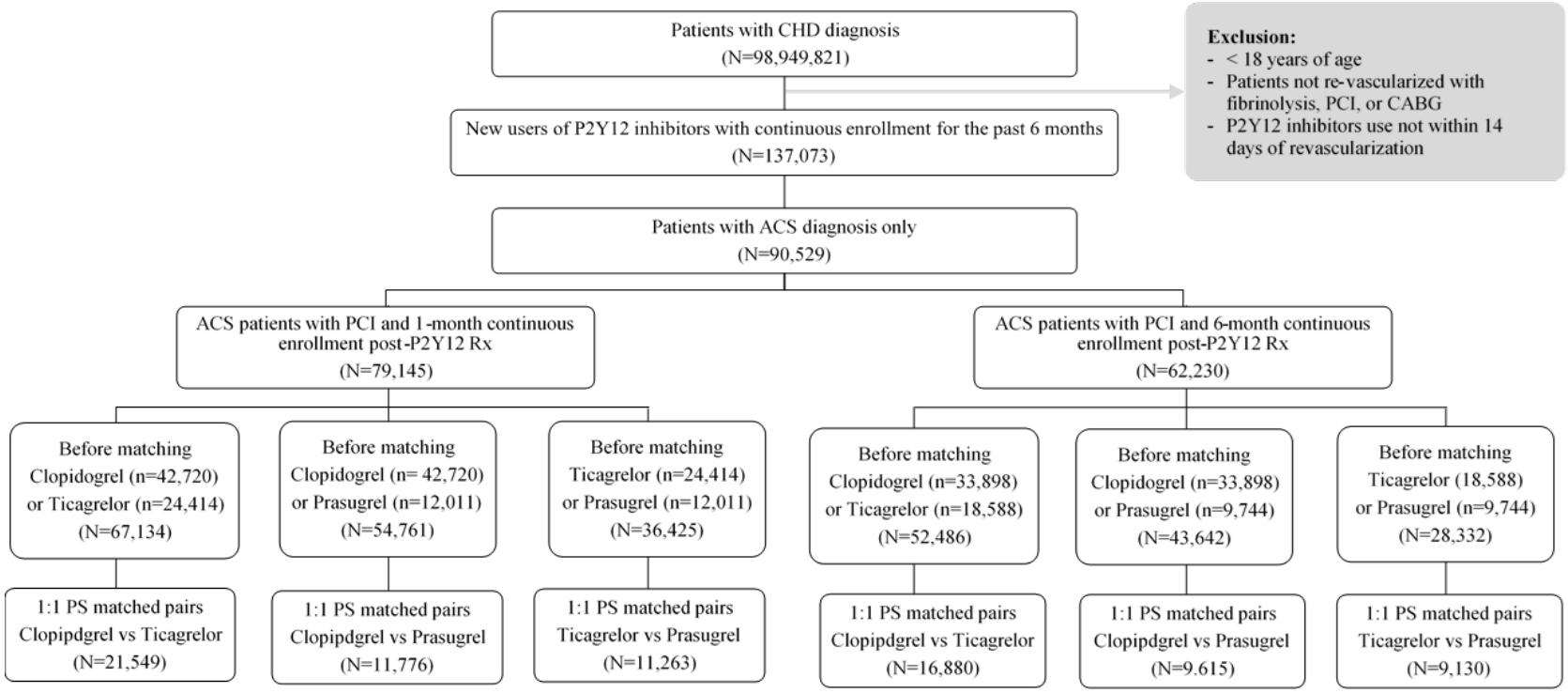
Appendix Table 4. 12 Number of Events, Cumulative Incidence, and Absolute Risk Difference for Secondary Effectiveness Outcomes in 1:1 PS-Matched Comparisons

P2Y12 inhibitor	Number of events	Total number of patients	Cumulative Incidence	Absolute Risk Difference	% Absolute Risk Difference
Cardiac Events Only					
30 days outcomes PS Matched Comparisons					
Clopidogrel versus Ticagrelor (PS Match (1: 1))					
Clopidogrel	434	21549	0.020140146	0.000139218	0.01392176
Ticagrelor	437	21549	0.020279363		
Clopidogrel versus Prasugrel (PS Match (1: 1))					
Clopidogrel	191	11776	0.016219429	8.49185E-05	0.008491848
Prasugrel	192	11776	0.016304348		
Ticagrelor versus Prasugrel (PS Match (1: 1))					
Ticagrelor	215	11263	0.019089053	-0.002663589	-0.266358874
Prasugrel	185	11263	0.016425464		
180 days outcomes PS Matched Comparisons					
Clopidogrel versus Ticagrelor (PS Match (1: 1))					
Clopidogrel	653	16880	0.038684834	0.001540284	0.154028436
Ticagrelor	679	16880	0.040225118		
Clopidogrel versus Prasugrel (PS Match (1: 1))					
Clopidogrel	353	9615	0.036713469	-0.000416017	-0.041601664
Prasugrel	349	9615	0.036297452		
Ticagrelor versus Prasugrel (PS Match (1: 1))					
Ticagrelor	371	9130	0.040635268	-0.003833516	-0.383351588
Prasugrel	336	9130	0.036801752		
Stroke Events Only					
30 days outcomes PS Matched Comparisons					
Clopidogrel versus Ticagrelor (PS Match (1: 1))					
Clopidogrel	22	21549	0.001020929	-0.000417653	-0.041765279
Ticagrelor	13	21549	0.000603276		
Clopidogrel versus Prasugrel (PS Match (1: 1))					
Clopidogrel	7	11776	0.000594429	0	0
Prasugrel	7	11776	0.000594429		
Ticagrelor versus Prasugrel (PS Match (1: 1))					
Ticagrelor	7	11263	0.000621504	0	0
Prasugrel	7	11263	0.000621504		
180 days outcomes PS Matched Comparisons					
Clopidogrel versus Ticagrelor (PS Match (1: 1))					
Clopidogrel	51	16880	0.003021327	-0.000829384	-0.082938389
Ticagrelor	37	16880	0.002191943		
Clopidogrel versus Prasugrel (PS Match (1: 1))					
Clopidogrel	25	9615	0.002600104	-0.000520021	-0.05200208
Prasugrel	20	9615	0.002080083		
Ticagrelor versus Prasugrel (PS Match (1: 1))					

Ticagrelor	19	9130	0.002081051	0	0
Prasugrel	19	9130	0.002081051		
Heart Failure Events Only					
30 days outcomes PS Matched Comparisons					
Clopidogrel versus Ticagrelor (PS Match (1: 1))					
Clopidogrel	199	21549	0.009234767	0.000278435	0.027843519
Ticagrelor	205	21549	0.009513202		
Clopidogrel versus Prasugrel (PS Match (1: 1))					
Clopidogrel	95	11681	0.008132865	0	0
Prasugrel	95	11681	0.008132865		
Ticagrelor versus Prasugrel (PS Match (1: 1))					
Ticagrelor	100	11263	0.008878629	-0.000621504	-0.062150404
Prasugrel	93	11263	0.008257125		
180 days outcomes PS Matched Comparisons					
Clopidogrel versus Ticagrelor (PS Match (1: 1))					
Clopidogrel	481	16880	0.028495261	-0.000829384	-0.082938389
Ticagrelor	467	16880	0.027665877		
Clopidogrel versus Prasugrel (PS Match (1: 1))					
Clopidogrel	236	9615	0.024544982	-0.002080083	-0.20800832
Prasugrel	216	9615	0.022464899		
Ticagrelor versus Prasugrel (PS Match (1: 1))					
Ticagrelor	371	9130	0.040635268	-0.003833516	-0.383351588
Prasugrel	336	9130	0.036801752		
PAD Events Only					
30 days outcomes PS Matched Comparisons					
Clopidogrel versus Ticagrelor (PS Match (1: 1))					
Clopidogrel	15	21549	0.000696088	-0.000278435	-0.027843519
Ticagrelor	9	21549	0.000417653		
Clopidogrel versus Prasugrel (PS Match (1: 1))					
Clopidogrel	9	11776	0.000764266	-0.000594429	-0.059442935
Prasugrel	2	11776	0.000169837		
Ticagrelor versus Prasugrel (PS Match (1: 1))					
Ticagrelor	1	11263	8.87863E-05	8.87863E-05	0.008878629
Prasugrel	2	11263	0.000177573		
180 days outcomes PS Matched Comparisons					
Clopidogrel versus Ticagrelor (PS Match (1: 1))					
Clopidogrel	38	16880	0.002251185	-0.00035545	-0.035545024
Ticagrelor	32	16880	0.001895735		
Clopidogrel versus Prasugrel (PS Match (1: 1))					
Clopidogrel	19	9615	0.001976079	-0.000832033	-0.083203328
Prasugrel	11	9615	0.001144046		
Ticagrelor versus Prasugrel (PS Match (1: 1))					
Ticagrelor	15	9130	0.001642935	-0.000547645	-0.054764513
Prasugrel	10	9130	0.00109529		

Note: *PSMATCH (1:1)* - propensity score matching (1:1) with nearest-neighbor matching technique without replacement

Appendix Figure 4. 1 Flowchart of Patients' Inclusion



Acronyms: CHD: coronary heart disease**,** PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, ACS: acute coronary syndrome, PS: a propensity score, P2Y12 Rx: prescription of either clopidogrel, prasugrel, or ticagrelor.

CHAPTER 5: STUDY 3

Comparative Risk of Hospitalized Bleeding of P2Y12 Inhibitors for Secondary Prophylaxis in Acute Coronary Syndrome after Percutaneous Coronary Intervention

5.1. Introduction

Following percutaneous coronary intervention (PCI), long-term management with oral P2Y12 inhibitors is essential in acute coronary syndrome (ACS) patients to prevent recurrent cardiovascular events.[202] The prophylaxis for recurrence of ACS events involves the use of dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor inhibitor (i.e., clopidogrel, prasugrel, or ticagrelor), as first-line therapy following a PCI.[15] Clopidogrel-based DAPT is hampered by its slow onset of action,[20] variable inter-individual response,[21] and treatment resistance,[22-24] resulting in a high risk of treatment failure. Newer P2Y12 inhibitors including prasugrel and ticagrelor have shown faster action and proven efficacy compared to clopidogrel.[25-29] Given better pharmacokinetic profiles, the use of newer P2Y12 inhibitor is recommended over clopidogrel, if not contraindicated [25,62]

Newer generation P2Y12 inhibitors have been shown to increase bleeding risk in randomized controlled trials (RCTs) following PCI. For example, in the TRITON-TIMI 38 trial,[118] the use of prasugrel resulted in a significantly higher risk of composite major bleeding compared to clopidogrel. The use of ticagrelor in the PLATO trial was not associated with overall major bleeding but did increase the rate of non-procedure-related bleeding and fatal intracranial bleeding compared to clopidogrel. However, the evidence of major bleeding risk from observational studies has been inconclusive with some

indicating higher and others indicating lower bleeding risk with newer generation P2Y12 inhibitors.[64-69] Much of this evidence in the US population comes from registries[30] or integrated healthcare records[64] which may be limited by their generalizability to a broader population, lack of medication use outside of a healthcare system, and incomplete data capture.[203] In addition to composite major bleeding risk, antiplatelet therapy to manage ACS patients has also been shown to cause life-threatening gastrointestinal (GI) bleeding, which is an independent predictor of mortality.[204,205] Several observational studies have shown clopidogrel to increase GI bleeding risk in both the upper and lower gastrointestinal tract.[206,207] Whereas, significant higher risk of GI bleeding in a meta-analysis of RCTs has been reported with newer P2Y12 inhibitors compared to clopidogrel..[148] Nevertheless, none of the studies have compared the risk of GI bleeding between newer P2Y12 inhibitors and clopidogrel in a real-world population.

Given that more than one million PCIs are performed every year in the US,[208] and availability of more potent P2Y12 inhibitors with inconsistent safety effects, it is imperative to study the burden of bleeding risk in a real-world population with P2Y12 inhibitors. Substantial rehospitalization within 30 days due to recurrent ACS events occurs in the US following PCI[184-188] that may need aggressive management with P2Y12 inhibitors. Because of the associated high bleeding risk with these drugs, assessment of safety is necessary for this high-risk period. Moreover, bleeding risk is also cited to be prevalent following 30 days of revascularization during the maintenance phase[209] that further necessitate the safety assessment while on prophylaxis.

The primary objective of this study was to study the comparative safety of P2Y12 inhibitors for ACS prophylaxis following PCI in terms of major bleeding and GI bleeding.

5.2. Methods

Data Source

This study was done using the IBM MarketScan® databases from January 1, 2013, to December 31st, 2018. These databases include a large population of more than 30-50 million commercially insured beneficiaries in the Commercial Claims and Encounters (CCAE) and 1 million Medicare beneficiaries with supplemental benefits in the Medicare Supplemental and Coordination of Benefits (MDCR) data set every year across the United States. The CCAE sample comprised patients aged 18 to 65 years. The MDCR sample included patients aged ≥ 65 years. These data contain de-identified person-level information on enrollment, linked to inpatient, outpatient, and prescription claims.

CCAE data contains information on healthcare coverage and service use of individuals under a variety of different insurance offerings including fee-for-service (FFS), capitated, preferred provider organization (PPO), health maintenance organization (HMO), and others. Whereas the MDCR database contains information on Medicare-eligible employees who have additional coverage through supplemental plans or employers. Similar to CCAE files, the MDCR database also contains information on healthcare coverage and service use of individuals under a variety of plan offerings. We combined IBM CCAE and MDCR data files to conduct this analysis.

Study Design

This study was conducted using a retrospective matched cohort study design in which we examined the comparative safety of three different P2Y12 inhibitors

(clopidogrel, ticagrelor, and prasugrel) following a PCI. We included patients with an age of at least 18 years discharged from the inpatient or outpatient setting with a diagnosis of ACS revascularized using PCI. A 6 month “run in” period was used as we wanted to focus on “new users” of P2Y12 inhibitors, and to identify comorbidities prior to PCI. Patients were excluded if they were not continuously enrolled with both medical and pharmacy benefits throughout the entire observational period.

Medication exposure was defined as the initiation of a P2Y12 inhibitor within 14 days of index PCI revascularization. Patients using P2Y12 inhibitors at any point prior to index PCI were excluded using an incident user study design. To identify ACS, we used validated international classification of disease 9 & 10 clinical modification codes (ICD-9 & 10-CM).[141-143] PCI procedures were coded using Current Diagnosis Procedure (CPT) codes, Healthcare Common Procedure Coding System (HCPCS), and ICD 9 and 10 procedure codes published previously.[69,161-164] The complete list of ICD, HCPCs, and CPT codes used is given in **Appendix Table 5.1**. All the drug claims in this study were identified by National Drug Code (NDC) from outpatient pharmacy claims data using the prescription fill date.

Three cohorts were constructed to compare the safety of (1) ticagrelor versus clopidogrel, (2) prasugrel versus clopidogrel, and (3) ticagrelor vs prasugrel. An intention to treat (ITT) approach was used, with participants remaining on the drug initially prescribed throughout the follow-up period. Patients were followed for incident hospitalized bleeding events for 30 and 180 days, respectively.

The schematic description of the study design and patient inclusion is depicted in **Figure 5.1** and **Appendix Figure 5.1**, respectively.

Outcome Variables

The primary safety outcome of major bleeding was determined using inpatient discharge codes for intracranial (IC), gastrointestinal (GI), and other serious forms of bleeding using the validated Cunningham algorithm[210]. IC bleeding was defined as subarachnoid and intracerebral hemorrhage as the primary discharge diagnosis. We defined GI bleeding, or any other serious form of bleeding (i.e., genitourinary, hemopericardium, hemoperitoneum, hemarthrosis, epistaxis, hemoptysis, hemorrhage from the throat, and unspecified hemorrhage) using primary and secondary discharge diagnosis along with transfusion codes in inpatient files. This bleeding definition had a positive predictive value between 89% to 99%.[210] In addition to reporting each major bleeding event separately, we use the composite “major bleeding” definition to identify any serious bleeding event throughout the manuscript. Similarly, we assessed the secondary safety outcomes as GI bleeding. We ended follow-up for these outcomes at 30 and 180 days after the index P2Y12 inhibitor prescription, respectively.

Substantial rehospitalization within 30 days due to recurrent ACS events occurs in the US following PCI[184-188] that may need aggressive management with P2Y12 inhibitors. Because of the associated high bleeding risk with these drugs, assessment of safety is necessary for this high-risk period. Moreover, bleeding risk is also cited to be prevalent following 30 days of revascularization during the maintenance phase[209] that further necessitate the safety assessment while on prophylaxis.

Although 12 months DAPT is recommended by AHA, a shorter 6 month duration of treatment has been associated with a lower risk of bleeding after PCI with drug-eluting stents (DES).[211] Given greater use of newer DES a shorter duration of P2Y12 treatment

may be appropriate for many patients. Hence, we studied the risk of bleeding across P2Y12 inhibitors during the first 6 months following a PCI to guide the use of these agents during this high-risk period. Furthermore, we studied the safety of P2Y12 inhibitors among patients at high risk of bleeding to examine safety outcomes in this high risk group

Confounding Variables

We grouped variables into three different categories based on (1) predisposing demographic, (2) enabling, and (3) need characteristics using Andersen's Behavioral Model (ABM) for Health Services Utilization.[134] This model incorporates both individual and contextual determinants of health care use.

(1) Predisposing variables included age, gender, and geographical region.
(2) Enabling characteristics that may facilitate the delivery of healthcare services were comprised of insurance plan/coverage variables in the data. These included exclusive provider organization (EPO), health maintenance organization (HMO), point-of-service (POS), preferred provider organization (PPO), consumer-driven health plan (CDHP), and high-deductible health plans (HDHP).
(3) Need variables represented both perceived and actual health condition mandates that may increase the need for treatment. This included the Elixhauser comorbidity index (EI) for readmission, high bleeding risk, and medication history. High bleeding risk was defined according to AHA guidelines[165] as (i) high-risk comorbidities in the past six months (i.e. diabetes mellitus, anemia, chronic kidney disease (CKD), and low body weight (LBW)) (ii) history of prior major bleeding (i.e., intracranial (IC), gastrointestinal (GI) and any other major

bleeding)), and (iii) concomitant use of high-risk medications (i.e., oral anticoagulants, Rx NSAIDs, or steroids). We defined concomitant use of drugs if any of these high-risk medications were filled (i) within 15 days before or (ii) within 30 days after the index dispensing day of a P2Y12 inhibitor. Patients were also required to have at least 30 days' supply of these high-risk medications to ensure concomitant use (overlap).

Statistical Analysis

Descriptive statistics were presented using counts and percentages for all of the pairwise comparisons. We made unadjusted comparisons using standardized difference testing to examine ABM variables (confounding variables described above) identified 6 months before index PCI. In order to control for confounding, we estimated a propensity score (PS) for likelihood of being prescribed a particular P2Y12 inhibitor for each patient using a multivariate logistic regression model. In this model, we incorporated group status as an outcome (e.g., clopidogrel initiators vs prasugrel initiators)) and potential treatment and outcomes predictors as control variables identified using ABM. Patients were matched 1:1 on their PS utilizing the nearest-neighbor matching technique without replacement within a caliper of 0.05.[150]

As this study included data from 2013 to 2018, we utilized exact matching to control for the year of treatment initiation. The exact match was used to control for the addition of new agents over time and changes in treatment adoption of these treatments. Using calendar time-specific PS matching is believed to have better control for confounding under these conditions.[194] Standardized differences were calculated to assess the balance of confounders at baseline for all of the PS matched comparisons.

An absolute standardized difference of ≤0.1 indicates a negligible difference in potential confounders and balanced matched cohorts.[195]

To perform time to event analysis, we utilized Cox-proportional hazards regression models to compare safety outcomes across different P2Y12 inhibitors over the 30 and 180 day follow-up time intervals. We ran these models before and after PS matching to examine the influence of matching on outcomes. Patients were followed until the outcome of interest was observed or administrative censoring due to reaching the follow-up time-frame of interest (30 or 180 days) or the end of the period for which data was available (December 31, 2018).

Hazard ratios (HRs) with their 95% confidence intervals (CIs) were used to present the results. The proportionality hazard assumption was tested by including an interaction term between exposure and time of follow-up. If there was any violation, we planned to run models stratified by follow-up time. Finally, we presented the cumulative incidence, person-days, and absolute risk differences (in percentage) for all the PS matched pairwise comparisons.

Subgroup Analyses

We analyzed the overall ACS population in the primary analysis and performed several subgroup analyses to look at differences in comparative safety in three separate groups with varying risk. These groups included patients with high bleeding risk, by sex[212], and with advanced age. We defined advanced age as patients with age at least 70 years as per POPular AGE trial.[46] We defined high bleeding risk according to AHA/ACC guidelines[165] that includes patients with (i) high-risk comorbidities in the past six months (i.e. diabetes mellitus, anemia, chronic kidney disease (CKD), and low body weight

(LBW)) (ii) history of prior major bleeding (i.e., intracranial (IC), gastrointestinal (GI) and any other major bleeding)), and (iii) concomitant use of high-risk medications (i.e., oral anticoagulants, Rx non-steroidal anti-inflammatory drugs (NSAIDs), or steroids). We defined concomitant use of drugs if any of these high-risk medications were filled (i) within 15 days before or (ii) within 30 days after the index dispensing day of a P2Y12 inhibitor. Patients were also required to have at least 30 days' supply of these high-risk medications to ensure concomitant use (overlap).

5.3. Results

Population Characteristics

For the 30-day outcomes **(Appendix Table 5.2)**, before matching, we identified 42,720, 24,414, and 12,011 patients who initiated clopidogrel, ticagrelor, and prasugrel within 14 days after the index PCI, respectively. Similarly, for 180-day outcomes, we observed 33,898, 18,588, and 9,744 patients on clopidogrel, ticagrelor, and prasugrel, respectively. On the 30th-day, before PS matching, we observed a higher use of prasugrel (76.4%) and ticagrelor (73.0%) over clopidogrel (59.1%) in the younger population i.e., 45-64 years age bracket; whereas, higher use of clopidogrel was observed in the older age brackets. Additionally, we observed increased use of clopidogrel with a higher comorbidity level. For example, with EI categories 3 and 4, we observed higher use of clopidogrel. Patients presenting with STEMI were prescribed newer P2Y12 inhibitors more often compared to NSTEMI/UA patients where clopidogrel was the choice of drug. Furthermore, we observed a higher prescription of clopidogrel (45.3%) compared to ticagrelor (37.6%) and prasugrel (35.6%) among the population at high risk of bleeding.

After PS matching, for the 30-day outcome cohort **(Appendix Table 5.3)**, we had 21,549 (clopidogrel versus ticagrelor), 11,776 (clopidogrel versus prasugrel), and 11,263 (ticagrelor versus prasugrel) matched pairs to compare outcome events in pairwise comparisons. For the clopidogrel vs ticagrelor matched pairs, the majority of the patients came from the 45-64 years age bracket (71.1% vs 70.8%), were predominantly males (74.0% vs 73.9%), and a higher number of patients had an EI of 0 (30.8% vs 31.5%) for the associated comorbidities. Importantly, a substantial number of patients

were at increased bleeding risk (39.2% vs 39.3%). Very similar characteristics for the other matched pairs (i.e. clopidogrel versus prasugrel and ticagrelor vs prasugrel) were observed at 30 days **(Appendix Table 5.3)**. A detailed description of all the PS matched comparisons at 30 and 180 days is given in **Appendix Tables 5.3 & 5.4.** For all the pairwise comparisons in this study, the standardized differences were less than 10% indicating well-balanced cohorts for the effectiveness outcomes comparisons.

Comparative Safety

Before PS matching **(Table 5.1)**, we observed 138 (0.32%), 53 (0.22%), and 27 (0.22%) patients with composite major bleeding events in the clopidogrel (n=42,720), ticagrelor (24,414), and prasugrel (12,011) group, respectively in 30 days. Also, in 180 days, we observed a substantial increase in the number of composite outcomes in each group, for example, in the clopidogrel group, the number of events increased from 138 (0.32%) to 337 (0.99%) from 30 days to 180 days. It should be noted that the composite outcome was comprised mainly of gastrointestinal bleeding events in all of these groups.

Risk of Composite Major Bleeding Events (Primary Safety Outcome)

1. **Clopidogrel vs ticagrelor users:** Before PS matching **(Table 5.2)**, ticagrelor was associated with a 33% reduced risk of composite major bleeding outcome (HR (95%CI): 0.67 (0.49-0.92)) compared to clopidogrel in 30 days. However, this effect was not significant after PS matching (HR (95%CI): 1.00 (0.68-1.48)). Similarly, at 180 days, we observed a significant 32% risk reduction (HR (95%CI): 0.68 (0.56-0.84)) associated with ticagrelor that was not found to be significant in PS matched comparisons (HR (95%CI): 0.83 (0.65-1.05)). For the absolute risk differences (ARD), on day 30 there was no difference between the groups after PS matching.

Whereas, on the 180th day, ticagrelor was associated with an ARD of 0.15% compared to clopidogrel **(Table 5.4)**.

In subgroup analyses **(Table 5.2)**, no differences between groups at high bleeding risk was seen at 30 days (HR (95%CI): 1.03 (0.62-1.74)) or 180 days (HR (95%CI): 0.99 (0.71-1.38)). Additionally, major bleeding risk was similar based on gender and advanced age at both time points.

2. **Clopidogrel vs prasugrel users:** Before matching **(Table 5.2)**, there was no difference between the groups for major bleeding at both follow-up times. There was also no difference in PS matched comparisons between the groups at 30 days (HR (95%CI): 0.90 (0.54-1.51)) or 180 days (HR (95%CI): 1.14 (0.83-1.56)). However, in PS matched comparisons, the ARD favored prasugrel i.e., 0.03% and 0.10% compared to clopidogrel **(Table 5.4)**. Subgroup analysis **(Table 5.2)** showed similar results as primary analysis.
3. **Ticagrelor vs prasugrel:** Similarly, we found no difference between the groups at both of the time points before PS matching **(Table 5.2)**. We continued to see no difference between the groups after PS matched comparisons in 30 days outcomes (HR (95%CI): 1.08 (0.63-1.86)). However, we observed a significant 44% increased major bleeding risk with prasugrel compared to ticagrelor (HR (95%CI): 1.44 (1.02-2.03)) in 180 day outcome. Additionally, prasugrel was associated with an ARD of 0.02% and 0.26% compared to ticagrelor at the 30 and 180 days of follow-up.

In the subgroup analysis, we found that the risk of major bleeding with prasugrel compared to ticagrelor was more pronounced among patients less than 70 years of age.

We report a significant 64% higher risk of hospitalization with major bleeding associated with prasugrel use compared to ticagrelor use among the patients ≤ 70 years.

Risk of Gastrointestinal Bleeding Events (Secondary Safety Outcome)

We observed very similar results **(Table 5.3)** as observed for composite major bleeding outcome except for the fact that prasugrel was associated with a 43% increased risk of GI bleeding compared to ticagrelor in before matching groups as well (HR (95%CI): 1.43 (1.04-1.99)). This risk remained consistent in PS matched analysis; we observed a 51% higher risk associated with prasugrel compared to ticagrelor (HR (95%CI): 1.51 (1.02-2.25)).

5.4. Discussion

In this real-world US population-based study (crude analysis), we observed that ticagrelor was associated with a 33% and 32% reduced risk of hospitalization due to major bleeding which included 'intracranial (IC)', 'gastrointestinal (GI)', and 'other bleeding' as a composite outcome compared to clopidogrel in 30 days and 180 days of follow-up, respectively. However, this difference no longer existed in PS matched comparisons for both of these follow-up times. Additionally, we observed no difference between prasugrel versus clopidogrel comparisons for crude and PS matched comparisons for 30 and 180 days outcomes. Furthermore, for prasugrel versus ticagrelor comparison, although there was no difference in major bleeding between groups at 30 days, prasugrel was associated with a 44% increased risk of hospitalizations due to major bleeding at 180 days. For the secondary safety outcome (GI bleeding), we observed similar results; there was no difference between ticagrelor versus clopidogrel and prasugrel versus clopidogrel in PS matched comparisons for 30 days and 180 days outcome. Nevertheless, prasugrel use was associated with a 51% higher risk of hospitalization due to GI bleeding compared to ticagrelor at 180 days.

Comparison between ticagrelor versus clopidogrel:

Ticagrelor is believed to have better platelet inhibition compared to clopidogrel. Unlike clopidogrel, it is a direct-acting $P2Y_{12}$-receptor antagonist that doesn't require metabolism to an active metabolite for efficacy.[14] Although ticagrelor has shown better efficacy in RCTs, in our study, we observed no difference in safety endpoints between ticagrelor and clopidogrel at 30 and 180 days in any subgroup examined. These results are consistent with the PLATO RCT[26] which showed no difference in major bleeding

between drugs. However, in this trial, although rare, fatal intracranial bleeding was noted more often with ticagrelor (0.1%) compared to clopidogrel (0.01%).

Prior observational studies show mixed evidence of bleeding risk comparing ticagrelor and clopidogrel. Recently, You et al. compared ticagrelor with clopidogrel in a retrospective analysis[64] using two different electronic health record (EHR) databases from the United States (OPTUM EHR and IQVIA Hospital data), and one database from South Korea (nationwide administrative claims database). This study reported a significantly higher risk of major bleeding associated with ticagrelor compared to clopidogrel in a pooled analysis (HR: 1.35; 95% CI (1.13-1.61)). It should be noted that this study considered only hemorrhagic stroke and GI bleeding events as their major bleeding definition that was different from our analysis. In another retrospective analysis based on a Canadian registry,[65] Turgeon et al., reported a significantly increased risk of major bleeding associated with ticagrelor compared to clopidogrel (aHR: 1.51; 95% CI (1.29-1.78)). Also, a significantly higher risk with ticagrelor was reported in a prospective cohort study by Sahlen et al. In this Swedish study, researchers used the data from the SWEDEHEART registry and reported a higher risk of readmission because of bleeding associated with ticagrelor (aHR: 1.20; 95% CI (1.04-1.40)) over a period of 24 months.

Nevertheless, a real-world analysis including data from various European contemporary registries reported lower event rates for bleeding with ticagrelor compared to clopidogrel over a period of 1 year.[68] However, there is evidence that both drugs are similar as far as bleeding risk is considered. For example, a Taiwanese study[213] that included 27,339 acute MI patients reported no difference between ticagrelor and clopidogrel for the major bleeding events over a follow-up time of 18 months (aHR:

0.731; 95% CI (0.522-1.026)). Additionally, a pre-post case-control study[67] based on a single-center registry also reported a similar risk of bleeding between ticagrelor and clopidogrel (OR: 1.45; 95% CI (0.65-3.21)).

Hence, there is mixed evidence in terms of the safety between ticagrelor and clopidogrel use in observational studies. The majority of evidence related to the safety of these drugs comes from countries other than the US, and results may not be applicable to the US population given that the ACS management may differ based on the practice patterns, healthcare system, and reimbursement policies for expensive drugs between different countries. However, the study by You et al. reported the comparative safety of these drugs in the US population and they presented a higher risk with ticagrelor compared to clopidogrel in the pooled analysis (HR: 1.35; 95% CI (1.13-1.61)). However, when the analysis was conducted separately for these two EHR databases, the results were different. For example, ticagrelor was not associated with higher bleeding risk (HR: 1.07; 95% CI (0.75-1.50)) in IQVIA Hospital data sample but was associated with higher bleeding risk in the sample from OPTUM EHR (HR: 1.34; 95% CI (1.10-1.63)). Also, the results of the You's study[64] may not be generalizable to the overall US population because of the limitation of EHR data in the sense that it lacks information outside of the healthcare system. Our study included the administrative data from a broad geographical area of the United States, which may better generalizable to the US population compared to the study by You et al.[64]

Comparison between prasugrel versus clopidogrel:

Comparing prasugrel to clopidogrel, we observed no difference in the risk of hospitalization due to bleeding at either 30 or 180 days. These results contrasted with

the results of the TRITON-TIMI trial[118] in which prasugrel use resulted in a high risk of both major bleeding (HR: 1.32; 95% CI (1.03-1.68)) and life-threatening intracranial bleeding. Our results are similar to a US-based real-world analysis conducted using the Premier Hospital Database (2009-2011) that reported no difference between the drugs at 30 days (OR:1.035; 95% CI (0.765-1.399)) and 90 days (OR:0.922; 95% CI (0.725-1.172)).[69] Another observational study (PROMETHEUS) based on the data from a registry (2010-2013) including 19,914 patients from 8 centers in the US reported similar safety of prasugrel and clopidogrel i.e., (OR: 1.03; 95% CI (0.78-1.36)) at 90 days and (OR: 0.97; 95% CI (0.78-1.22)) at 365 days.[30] Interestingly, a study utilizing a Swedish registry reported a lower risk of bleeding with prasugrel.[214] In this study prasugrel use was avoided among those at high risk of bleeding, which might have reduced bleeding risk. Yet, a prospective cohort study conducted in Switzerland[215] indicated no difference between composite bleeding events between the two groups (aHR: 0.63; 95% CI (0.39-1.03)). This study indicated that most of the bleeding events occurred during the first 30 days indicating the importance of safety outcomes assessment at 30 days following invasive management of ACS events. However, a network meta-analysis showed that prasugrel was associated with a 26% higher odds of major bleeding compared to clopidogrel (OR: 1.26; 95% CI (1.01-1.56))[216]. Thus, the evidence from observational studies is conflicting regarding the safety risk with these medications.

Similar to ticagrelor, the comparative safety evidence for prasugrel and clopidogrel in the US also comes from observational studies conducted using data registries or EHR data that may only represent the population from a particular healthcare system and may not be generalizable to the entire US population. Our study evaluated the risk of bleeding in the US population among different payers and various

regions in the US using claims data. We present the most current evidence related to the comparative safety of prasugrel with clopidogrel in the US population since 2013[30]

Comparison between prasugrel versus ticagrelor:

Our results suggest a slightly higher bleeding risk with prasugrel compared to ticagrelor for both primary and secondary safety endpoints. Nevertheless, the risk of composite major bleeding and GI bleeding was only significant at 180 days. We observed a 44% (composite major bleeding) and 51% (GI bleeding) higher risk associated with prasugrel compared to ticagrelor. It is important to note that this difference was age related **(Table 5.2)**. We found that among patients <70 years of age prasugrel use was associated with a 64% higher risk of bleeding compared to clopidogrel. This difference may be driven in part by the channeling of prescribing to at-risk populations. For example, up to 90% of the population who was prescribed prasugrel or ticagrelor in our sample were less than 70 years old.

A lower risk of major bleeding in 30 days follow-up time (Relative Risk: 0.65; 95% CI, 0.45-0.95)) has also been reported with prasugrel compared to ticagrelor,[217] with another study indicating higher risk with ticagrelor up to 1 year of follow-up time (3.8% versus 1.7%;p=0.04)[198] Nevertheless, in a network meta-analysis (indirect comparison) including 12 studies with 52,816 patients, ticagrelor and prasugrel were shown to have similar safety in terms of bleeding events. Similar to our study, another US-based observational study (2011-2016) using MarketScan data reported better safety with ticagrelor use over prasugrel in terms of major bleeding (HR: 0.54 95% CI (0.41-0.70)).[143] However, this study considered overall ACS patients regardless of whether patients were revascularized or not different than our study in which we included ACS

patients undergoing a PCI. We also measured outcomes in the high-risk period i.e., 30 days and 180 days for which antiplatelet therapy is recommended by AHA. Furthermore, we present the most current evidence not only among the overall ACS patients but also the safety risk among the patients at high risk of major bleeding.

Comparison of event rates with pivotal clinical trials:

Importantly, the number of major bleeding events in our study was far less compared to those reported in RCTs. For instance, major bleeding events in ticagrelor and clopidogrel in the PLATO trial were 11.6% and 11.2%, respectively; whereas, in our study, we observed only 0.8% and 0.7% major bleeding events in 180 days **(Table 5.4)** with these drugs, respectively. The lower number of bleeding events reported in our study may stem from identification in hospital claims alone. This definition increases confidence that the bleeding event was severe, as it resulted in a hospital admission, but may exclude bleeding events identified in the outpatient setting. Our results are similar to another observational study[64] that used claims data similar to ours' study and reported the bleeding events to be very rare. For example, this study reported GI bleeding events to be only 0.9% with clopidogrel and 1.2% with ticagrelor and reported no difference over a follow-up period of one year. Additionally, in a European study that used data from 12 registries,[218] life-threatening bleeding was reported to be very rare as well i.e. 0.08 to 0.13% with these drugs.

It is crucial to note that this variability in the event rates may also be due to the discrepancies in the definitions to define major bleeding in different studies. The variability in definitions of bleeding has been discussed in the past as a potential factor in the inconsistency of reported event rates in different RCTs comparing P2Y12 inhibitors

in ACS patients. For example, in TRITON-TIMI 38 trial,[118] major bleeding events were reported to be 1.8% among clopidogrel users over 15 months; whereas, in the PLATO trial,[26] major bleeding was reported to be 11.2% with clopidogrel over a span of 12 months. In a study by Quinlan et al, when a standardized definition to compare various RCTs comparing P2Y12 inhibitors was tested, the difference in the reported event rates in the trials comparing these agents was attenuated.[219] Thus, there is a need to study the impact of various bleeding definitions used in observational studies on the major bleeding outcomes by future researchers.

In our study, we present the most current evidence in the US population in which we studied the difference between the safety of ticagrelor and prasugrel compared to clopidogrel at 30 and 180 days. The results of our study are of particular clinical interest as the 30 days following revascularization are associated with high rates of hospital readmissions[185-188] indicating a need for aggressive platelet inhibition during this period for better clinical outcomes. This study has a significant policy implication as we present no difference in readmission rates because of major bleeding between clopidogrel, and the newer P2Y12 inhibitors prasugrel and ticagrelor. Given a lack of difference in safety events, it should be noted that the cost of clopidogrel is significantly less than newer agents which could also influence prescribing patterns for the management of ACS post PCI.

Strengths and Limitations

This study has various strengths. First, the sample size of P2Y12 inhibitors use was large which enabled us to examine safety outcomes across a number of factors including baseline bleeding risk, age, and gender. The size of the population studied

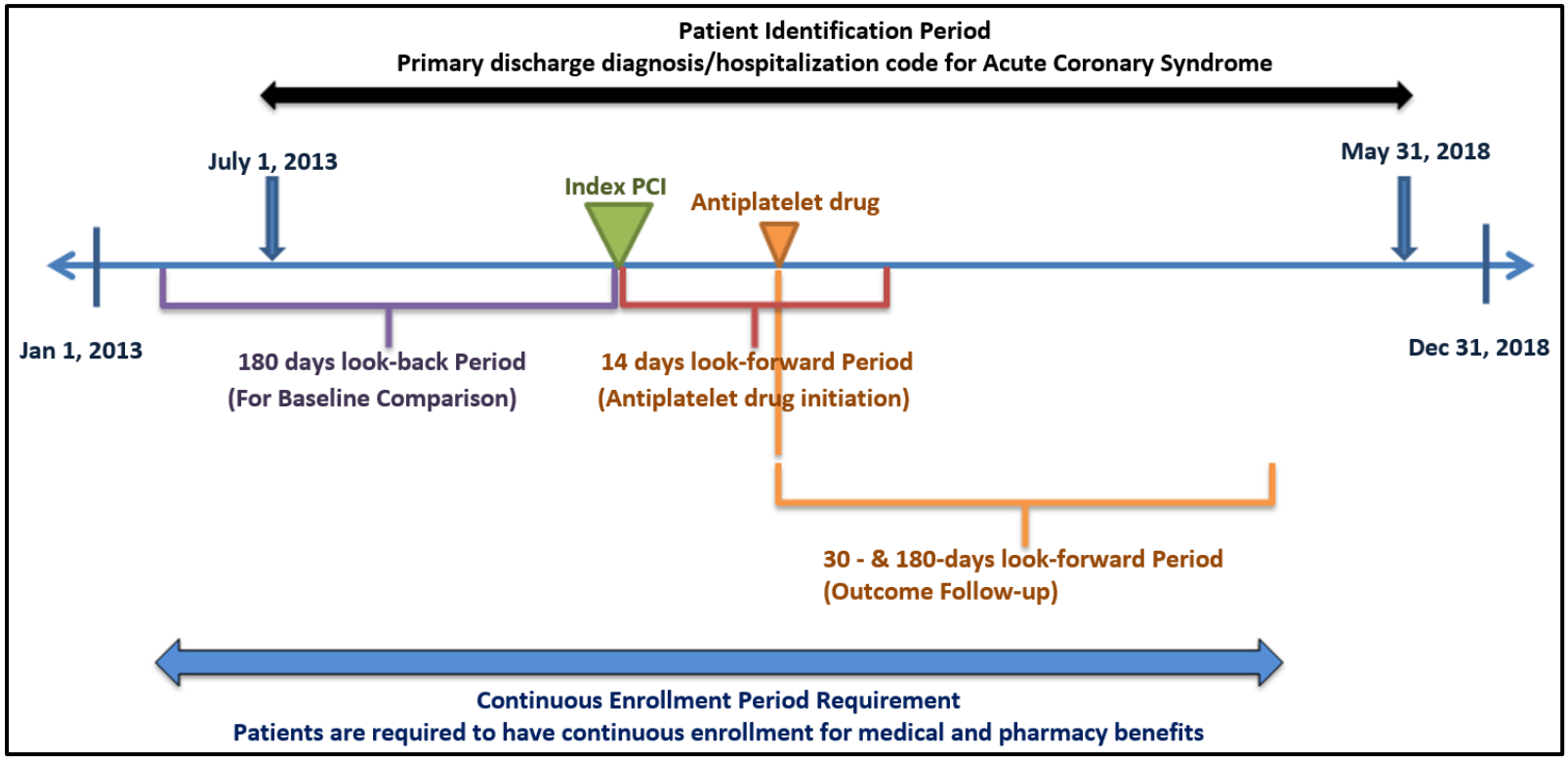
also allowed us to propensity match treatment groups across numerous clinical factors such as v age, sex, region, plan types, comorbidity conditions, high bleeding risk, and previous medication history using the ABM model to reduce the risk of confounding. Secondly, comparisons made between P2Y12 inhibitors for secondary ACS prophylaxis provides guidance for clinical practice that is often not available during the drug approval process. Using the most current data available, these data provide important guidance for the appropriate management of ACS in the US.

This study also has several limitations. Although various important clinical variables were used to control for the confounding, residual confounding may occur due to the observational nature of the study. While validated algorithms were used to identify incident ACS events, associated comorbidities of interest and bleeding outcomes, misclassification may occur. We were not able to study the role of aspirin on the comparative safety of P2Y12 inhibitors as MarketScan data doesn't capture over-the-counter aspirin use. We didn't have access to patients' laboratory values, socioeconomic status, race, ethnicity, and formulary preference which might act as confounders. We didn't look at whether patients adhered to the medications prescribed as there is a chance that some patients might have switched to clopidogrel which is less expensive than newer P2Y12 inhibitors. Finally, the results of this study are only generalizable to the population from which the data are derived commercially insured patients and patients with Medicare supplemental benefits.

5.5. Conclusion

In this study, we found that compared to clopidogrel, ticagrelor and prasugrel were not associated with a better safety profile in terms of major bleeding (which included intracranial, gastrointestinal, or other forms of serious bleeding) at 30 days and 180 days follow-up. However, ticagrelor was found to be associated with a lower risk of serious bleeding compared to prasugrel at 180 days of follow-up. The result of this study presents the most current evidence in terms of safety across all the P2Y12 inhibitors most commonly used among the patients and will help in better decision-making while prescribing these medications. Given that we utilized hospitalizations due to serious bleeding as our bleeding outcome, future studies are warranted to study the serious outpatients bleeding events to know the magnitude of comparative risk of serious bleeding with these drugs in real world population.

Figure 5. 1 Scheme for Patient Selection



Acronym: PCI: percutaneous coronary intervention

Table 5. 1 Number of Major Bleeding Events in Each Group of P2Y12 Inhibitors Users before Propensity Score Matching

Number of events in each group before propensity score matching			
At 30 days			
Event	***Clopidogrel (N=42,720)***	***Ticagrelor (24,414)***	***Prasugrel (12,011)***
Major Bleeding	138 (0.32)	53 (0.22)	27 (0.22)
Gastrointestinal	106 (0.25)	37 (0.15)	20 (0.17)
Intracranial	6 (0.01)	2 (0.01)	2 (0.02)
Any other	27 (0.06)	14 (0.06)	5 (0.04)
At 180 days			
Event	***Clopidogrel (N=33,898)***	***Ticagrelor (N=18,588)***	***Prasugrel (N=9,744)***
Major Bleeding	337 (0.99)	126 (0.68)	82 (0.84)
Gastrointestinal	246 (0.73)	87 (0.47)	65 (0.67)
Intracranial	18 (0.05)	8 (0.04)	5 (0.05)
Any other	74 (0.22)	31 (0.17)	12 (0.12)

Note: Major bleeding: hospitalization due to intracranial or gastrointestinal or any other major bleeding.

Table 5. 2 Comparative Risk of Composite Major Bleeding Outcomes (Primary Safety Outcomes) Before and After Propensity Score Matching

Composite Major Bleeding Events			
	Ticagrelor vs Clopidogrel (Hazard Ratios (95% CI))	**Prasugrel vs Clopidogrel** (Hazard Ratios (95% CI))	**Prasugrel vs Ticagrelor** (Hazard Ratios (95% CI))
At 30 days			
Before PS Matching			
Crude Analysis	**0.67 (0.49-0.92)**	0.70 (0.46-1.05)	1.04 (0.65-1.65)
After PS Matching			
Primary Analysis	1.00 (0.68-1.48)	0.90 (0.54-1.51)	1.08 (0.63-1.86)
Sub Group Analysis			
Bleeding Risk			
High Bleeding risk	1.03 (0.62-1.74)	0.64 (0.31-1.34)	0.84 (0.39-1.82)
Gender			
Males	1.00 (0.63- 1.60)	0.83 (0.45-1.53)	1.06 (0.56-2.02)
Females	0.99 (0.49 2.04)	1.12 (0.41-3.09)	1.13 (0.41- 3.13)
Advanced Age			
< 70 Years	1.12 (0.71-1.75)	0.92 (0.51-1.65)	0.93 (0.52-1.67)
>= 70 Years	0.71 (0.31-1.64)	1.01 (0.32-3.17)	3.21 (0.62-16.51)
At 180 days			
Before PS Matching			
	0.68 (0.56 0.84)	0.85 (0.67 1.08)	1.24 (0.94 1.64)
After PS Matching			
Primary Analysis	0.83 (0.65-1.05)	1.14 (0.83 1.56)	**1.44 (1.02-2.03)**
Sub Group Analysis			
Bleeding Risk			
High Bleeding risk	0.99 (0.71 1.38)	1.22 (0.74 2.02)	1.01 (0.62-1.64)
Gender			
Males	0.886 0.660 1.188	1.145 0.791 1.657	1.468 0.977 2.205
Females	0.704 0.454 1.092	1.113 0.602 2.056	1.364 0.716 2.597
Advanced Age			
< 70 Years	0.86 (0.64-1.15)	1.24 (0.86-1.78)	**1.64 (1.09-2.44)**
>= 70 Years	0.80 (0.52-1.23)	1.07 (0.55-2.08)	1.18 (0.59-2.35)

Note: Major bleeding: hospitalization due to intracranial or gastrointestinal or any other major bleeding.

Table 5. 3 Comparative Risk of Composite Gastrointestinal Bleeding Outcomes (Secondary Safety Outcomes) Before and After Propensity Score Matching

	Ticagrelor vs Clopidogrel (Hazard Ratios (95% CI))	**Prasugrel vs Clopidogrel** (Hazard Ratios (95% CI))	**Prasugrel vs Ticagrelor** (Hazard Ratios (95% CI))
At 30 days			
Before PS Matching			
Primary Analysis	**0.61 (0.42 0.89)**	0.67 (0.42 1.08)	1.10 (0.64 1.89)
After PS Matching			
Primary Analysis	0.95 (0.60 1.50)	0.87 (0.48 1.58)	1.05 (0.56 1.97)
At 180 days			
Before PS Matching			
Primary Analysis	**0.64 (0.51 0.82)**	0.92 (0.70 1.21)	**1.43 (1.04 1.99)**
After PS Matching			
Primary Analysis	0.76 (0.57 1.02)	1.23 (0.85 1.76)	**1.51 (1.02 2.25)**

Table 5. 4 Number of Events, Cumulative Incidence, Absolute Risk Difference, and Person Days for Composite Major Bleeding Outcomes in 1:1 PS-Matched Comparisons

P2Y12 inhibitor	Number of events	Total number of patients	Cumulative Incidence	Person Days	% Absolute Risk Difference
Composite Major Bleeding Outcome					
30 days outcomes PS Matched Comparisons					
Clopidogrel versus Ticagrelor					
Clopidogrel	50	21,549	0.002320293	645598	0
Ticagrelor	50	21,549	0.002320293	645592	
Clopidogrel versus Prasugrel					
Clopidogrel	30	11,776	0.002547554	352808	-0.025475543
Prasugrel	27	11,776	0.002292799	352889	
Ticagrelor versus Prasugrel					
Ticagrelor	25	11,263	0.002219657	337433	0.017757258
Prasugrel	27	11,263	0.00239723	337499	
180 days outcomes PS Matched Comparisons					
Clopidogrel versus Ticagrelor					
Clopidogrel	143	16,880	0.008471564	3024613	-0.148104265
Ticagrelor	118	16,880	0.006990521	3026506	
Clopidogrel versus Prasugrel					
Clopidogrel	72	9,615	0.0074883	1723280	0.10400416
Prasugrel	82	9,615	0.008528341	1721688	
Ticagrelor versus Prasugrel					
Ticagrelor	55	9,130	0.006024096	1637680	0.26286966
Prasugrel	79	9,130	0.008652793	1634792	

5.6. Supplementary Materials

Appendix Table 5. 1 ICD 9 & 10 CM and CPT Codes for Identification of Events and Outcomes

Cohort Selection	
Acute Coronary Syndrome (Any Position)	**Acute Myocardial Infarction:** **ICD-9 CM:** 410, 410.0, 410.00, 410.01, 410.1, 410.10, 410.11, 410.2, 410.20, 410.21, 410.3, 410.30, 410.31, 410.4, 410.40, 410.41, 410.5, 410.50, 410.51, 410.6, 410.60, 410.61, 410.7, 410.70, 410.71, 410.8, 410.80, 410.81, 410.9, 410.90, 410.91 **ICD-10 CM:** I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I21.4, R9430, R9431 **Unstable Angina:** **ICD-9 CM:** 411, 411.0, 411.1, 411.8, 411.81, 411.89 **ICD-10 CM:** I20.0, I24, I24.0, I24.1, I24.8, I24.9, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790
Percutaneous Coronary Intervention (PCI) (Any position):	**ICD 9 Procedure codes:** '0066' '3601' '3602' '3603' '3605' '3606' '3607' '3609' **ICD 10 Procedure codes:** '0270346' '027034Z' '0270356' '027035Z' '0270366' '027036Z' '0270376' '027037Z' '02703D6' '02703DZ' '02703ZZ' '0270046' '0271346' '027134Z' '0271356' '027135Z' '0271366' '027136Z' '0271376' '027137Z' '02713D6' '02713DZ' '02714E6' '02713EZ' '02714EZ' '02723FZ' '02733GZ' '02713E6' '02723F6' '02733G6' '0272366' '0273376' '027236Z' '027337Z' '02C03ZZ' '02C13ZZ' '02C23ZZ' '02C33ZZ' '02C03Z6' '02C13Z6' '02C23Z6' '02C33Z6' '92980' '92981' '92982' '92984' '92920' '92924' '92925' '92921' '92928' '92929' '92933' '92934' '37184' '37185' '37186' '37187' '37188' 'C9600' 'C9601' 'C9602' 'C9603' 'G0290' 'G0291'

Acronyms: ICD 9 & 10 CM codes**:** international classification of disease 9 & 10 clinical modification codes, CPT: current diagnosis procedure codes

Appendix Table 5. 2 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users before Propensity Score Matching

Variable	30 Day			180 Day		
	Clopidogrel N = 42,720	Ticagrelor N = 24,414	Prasugrel N = 12,011	Clopidogrel N = 33,898	Ticagrelor N = 18,588	Prasugrel N = 9,744
AGE CATEGORY						
18-44 Years	2,242 (5.2%)	1,873 (7.7%)	994 (8.3%)	1,757 (5.2%)	1,366 (7.3%)	795 (8.2%)
45-64 Years	25,255 (59.1%)	17,821 (73%)	9,174 (76.4%)	19,932 (58.8%)	13,487 (72.6%)	7,494 (76.9%)
65-84 Years	13,052 (30.6%)	4,353 (17.8%)	1,798 (15%)	10,470 (30.9%)	3,430 (18.5%)	1,419 (14.6%)
85 Years & Above	2,171 (5.1%)	367 (1.5%)	45 (0.4%)	1,739 (5.1%)	305 (1.6%)	36 (0.4%)
SEX						
Male	29,991 (70.2%)	18,258 (74.8%)	9,358 (77.9%)	23,862 (70.4%)	13,926 (74.9%)	7,614 (78.1%)
Female	12,729 (29.8%)	6,156 (25.2%)	2,653 (22.1%)	10,036 (29.6%)	4,662 (25.1%)	2,130 (21.9%)
REGION						
Northeast	8,614 (20.2%)	4,978 (20.4%)	2,009 (16.7%)	6,890 (20.3%)	3,854 (20.7%)	1,632 (16.7%)
North Central	12,286 (28.8%)	6,186 (25.3%)	2,548 (21.2%)	9,863 (29.1%)	4,797 (25.8%)	2,132 (21.9%)
South	15,733 (36.8%)	10,547 (43.2%)	5,759 (47.9%)	12,515 (36.9%)	7,951 (42.8%)	4,698 (48.2%)
West	5,707 (13.4%)	2,549 (10.4%)	1,530 (12.7%)	4,371 (12.9%)	1,876 (10.1%)	1,177 (12.1%)
Other	380 (0.9%)	154 (0.6%)	165 (1.4%)	259 (0.8%)	110 (0.6%)	105 (1.1%)
PLAN TYPE						
Comprehensive	7,437 (17.4%)	2,300 (9.4%)	1,180 (9.8%)	6,202 (18.3%)	1,841 (9.9%)	996 (10.2%)
EPO	305 (0.7%)	207 (0.8%)	107 (0.9%)	231 (0.7%)	151 (0.8%)	82 (0.8%)
HMO	4,641 (10.9%)	2,313 (9.5%)	1,132 (9.4%)	3,522 (10.4%)	1,761 (9.5%)	880 (9%)
POS	2,476 (5.8%)	1,597 (6.5%)	751 (6.3%)	1,911 (5.6%)	1,109 (6%)	609 (6.3%)
PPO	22,091 (51.7%)	13,185 (54%)	6,796 (56.6%)	17,607 (51.9%)	10,113 (54.4%)	5,542 (56.9%)
POS with Capitation	384 (0.9%)	265 (1.1%)	80 (0.7%)	301 (0.9%)	207 (1.1%)	63 (0.6%)
CDHP	2,835 (6.6%)	2,542 (10.4%)	1,086 (9%)	2,343 (6.9%)	1,998 (10.7%)	941 (9.7%)
HDHP	1,779 (4.2%)	1,509 (6.2%)	646 (5.4%)	1,350 (4%)	1,116 (6%)	506 (5.2%)
ELIXHAUSER INDEX						
Category 0	11,928 (27.9%)	7,788 (31.9%)	3,682 (30.7%)	9,555 (28.2%)	5,942 (32%)	2,993 (30.7%)

Variable	30 Day			180 Day		
	Clopidogrel N = 42,720	**Ticagrelor N = 24,414**	**Prasugrel N = 12,011**	**Clopidogrel N = 33,898**	**Ticagrelor N = 18,588**	**Prasugrel N = 9,744**
Category 1	10,859 (25.4%)	6,631 (27.2%)	3,744 (31.2%)	8,982 (26.5%)	5,260 (28.3%)	3,171 (32.5%)
Category 2	2,960 (6.9%)	1,815 (7.4%)	771 (6.4%)	2,310 (6.8%)	1,331 (7.2%)	607 (6.2%)
Category 3	9,335 (21.9%)	4,923 (20.2%)	2,504 (20.8%)	7,356 (21.7%)	3,667 (19.7%)	1,997 (20.5%)
Category 4	7,638 (17.9%)	3,257 (13.3%)	1,310 (10.9%)	5,695 (16.8%)	2,388 (12.8%)	976 (10%)
ACS TYPE						
STEMI	12,967 (30.4%)	9,275 (38%)	4,503 (37.5%)	10,402 (30.7%)	7,155 (38.5%)	3,697 (37.9%)
NSTEMI/UA	24,869 (58.2%)	12,751 (52.2%)	6,281 (52.3%)	19,766 (58.3%)	9,698 (52.2%)	5,110 (52.4%)
BLEEDING RISK						
High Bleeding Risk	19,371 (45.3%)	9,225 (37.8%)	4,381 (36.5%)	15,077 (44.5%)	6,875 (37%)	3,471 (35.6%)
MEDICATION HISTORY						
Anti-Diabetics						
Antidiabetics (Miscellaneous: *Biguanides, GLP-1 analogues DPP4, alpha-glucoside inhibitors, incretin mimetics, amylin analogues, glucagon, and combinations*)	7,467 (17.5%)	4,128 (16.9%)	2,074 (17.3%)	5,846 (17.2%)	3,098 (16.7%)	1,624 (16.7%)
Meglitinide	143 (0.3%)	56 (0.2%)	27 (0.2%)	110 (0.3%)	42 (0.2%)	22 (0.2%)
SGLT Inhibitors	630 (1.5%)	575 (2.4%)	224 (1.9%)	478 (1.4%)	406 (2.2%)	172 (1.8%)
Sulfnylureas	3,480 (8.1%)	1,638 (6.7%)	797 (6.6%)	2,726 (8%)	1,230 (6.6%)	622 (6.4%)
TZDs	472 (1.1%)	264 (1.1%)	145 (1.2%)	367 (1.1%)	200 (1.1%)	117 (1.2%)
Anti-Hypertensive						
ACE Inhibitors	10,727 (25.1%)	5,308 (21.7%)	2,735 (22.8%)	8,491 (25%)	4,007 (21.6%)	2,191 (22.5%)
Beta Blockers	16,076 (37.6%)	6,867 (28.1%)	3,610 (30.1%)	12,638 (37.3%)	5,229 (28.1%)	2,874 (29.5%)
Calcium Channel Blockers	9,144 (21.4%)	4,241 (17.4%)	1,911 (15.9%)	7,198 (21.2%)	3,240 (17.4%)	1,498 (15.4%)
ARBs	8,071 (18.9%)	4,233 (17.3%)	2,005 (16.7%)	6,368 (18.8%)	3,242 (17.4%)	1,599 (16.4%)

Variable	30 Day			180 Day		
	Clopidogrel N = 42,720	Ticagrelor N = 24,414	Prasugrel N = 12,011	Clopidogrel N = 33,898	Ticagrelor N = 18,588	Prasugrel N = 9,744
Diuretics						
Loop Diuretics	4,040 (9.5%)	1,199 (4.9%)	568 (4.7%)	3,096 (9.1%)	903 (4.9%)	444 (4.6%)
Potassium Sparing Diuretics	1,754 (4.1%)	657 (2.7%)	348 (2.9%)	1,344 (4%)	497 (2.7%)	280 (2.9%)
Thiazide Diuretics	3,418 (8%)	1,620 (6.6%)	793 (6.6%)	2,729 (8.1%)	1,198 (6.4%)	618 (6.3%)
Other Medications						
Anti-Platelets	4,900 (11.5%)	2,228 (9.1%)	1,325 (11%)	3,798 (11.2%)	1,661 (8.9%)	998 (10.2%)
Anti-Arrhythmics	740 (1.7%)	163 (0.7%)	90 (0.7%)	546 (1.6%)	125 (0.7%)	67 (0.7%)
Anti-Hyperlipidimics	20,368 (47.7%)	10,160 (41.6%)	5,309 (44.2%)	16,064 (47.4%)	7,697 (41.4%)	4,256 (43.7%)
Anti-Depressants	7,822 (18.3%)	4,005 (16.4%)	1,984 (16.5%)	6,058 (17.9%)	2,993 (16.1%)	1,592 (16.3%)
Estrogens	770 (1.8%)	372 (1.5%)	208 (1.7%)	606 (1.8%)	296 (1.6%)	163 (1.7%)
PPIs	9,084 (21.3%)	4,376 (17.9%)	2,207 (18.4%)	7,131 (21%)	3,331 (17.9%)	1,729 (17.7%)
H2RAs	1,438 (3.4%)	665 (2.7%)	277 (2.3%)	1,132 (3.3%)	510 (2.7%)	220 (2.3%)

Acronyms: EPO: Exclusive Provider Organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: Non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: Sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 5. 3 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users after Propensity Score Matching at 30 Days

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 Days			Clopidogrel : Prasugrel (1:1 PS Match) 30 Days			Ticagrelor : Prasugrel (1:1 PS Match) 30 Days		
Variable	**Clopidogrel N = 21,549**	**Ticagrelor N = 21,549**	**SDs**	**Clopidogrel N = 11,776**	**Prasugrel N = 11,776**	**SDs**	**Ticagrelor N = 11,263**	**Prasugrel N = 11,263**	**SDs**
AGE CATEGORY									
18-44 Years	1,470 (6.8%)	1,646 (7.6%)	-0.0310	925 (7.9%)	968 (8.2%)	-0.0110	866 (7.7%)	924 (8.2%)	-0.0185
45-64 Years	15,321 (71.1%)	15,255 (70.8%)	0.0066	8,980 (76.3%)	8,981 (76.3%)	0.0000	8,545 (75.9%)	8,548 (75.9%)	0.0000
65-84 Years	4,378 (20.3%)	4,293 (19.9%)	0.0100	1,825 (15.5%)	1,782 (15.1%)	0.0111	1,805 (16%)	1,747 (15.5%)	0.0137
85 years & Above	380 (1.8%)	355 (1.6%)	0.0155	46 (0.4%)	45 (0.4%)	0.0000	47 (0.4%)	44 (0.4%)	0.0000
SEX									
Male	15,941 (74%)	15,930 (73.9%)	0.0023	9,233 (78.4%)	9,178 (77.9%)	0.0121	8,777 (77.9%)	8,755 (77.7%)	0.0048
Female	5,608 (26%)	5,619 (26.1%)	-0.0023	2,543 (21.6%)	2,598 (22.1%)	-0.0121	2,486 (22.1%)	2,508 (22.3%)	-0.0048
REGION									
Northeast	4,329 (20.1%)	4,404 (20.4%)	-0.0075	1,964 (16.7%)	1,908 (16.2%)	0.0135	1,840 (16.3%)	1,848 (16.4%)	-0.0027
North Central	5,697 (26.4%)	5,492 (25.5%)	0.0205	2,560 (21.7%)	2,529 (21.5%)	0.0049	2,487 (22.1%)	2,467 (21.9%)	0.0048
South	9,012 (41.8%)	9,167 (42.5%)	-0.0142	5,617 (47.7%)	5,669 (48.1%)	-0.0080	5,420 (48.1%)	5,377 (47.7%)	0.0080
West	2,375 (11%)	2,333 (10.8%)	0.0064	1,490 (12.7%)	1,505 (12.8%)	-0.0030	1,389 (12.3%)	1,416 (12.6%)	-0.0091
Other	136 (0.6%)	153 (0.7%)	-0.0124	145 (1.2%)	165 (1.4%)	-0.0177	127 (1.1%)	155 (1.4%)	-0.0270
PLAN TYPE									
Comprehensive	2,325 (10.8%)	2,250 (10.4%)	0.0130	1,235 (10.5%)	1,180 (10%)	0.0165	1,099 (9.8%)	1,143 (10.1%)	-0.0100
EPO	173 (0.8%)	199 (0.9%)	-0.0109	95 (0.8%)	107 (0.9%)	-0.0109	89 (0.8%)	102 (0.9%)	-0.0109
HMO	2,168 (10.1%)	2,155 (10%)	0.0033	1,158 (9.8%)	1,132 (9.6%)	0.0068	1,062 (9.4%)	1,068 (9.5%)	-0.0034
POS	1,381 (6.4%)	1,455 (6.8%)	-0.0161	725 (6.2%)	751 (6.4%)	-0.0082	701 (6.2%)	731 (6.5%)	-0.0123
PPO	11,989 (55.6%)	11,703 (54.3%)	0.0261	6,763 (57.4%)	6,794 (57.7%)	-0.0061	6,577 (58.4%)	6,462 (57.4%)	0.0203
POS with capitation	242 (1.1%)	251 (1.2%)	-0.0094	71 (0.6%)	80 (0.7%)	-0.0124	75 (0.7%)	78 (0.7%)	0.0000
CDHP	2,020 (9.4%)	2,224 (10.3%)	-0.0302	1,080 (9.2%)	1,086 (9.2%)	0.0000	1,038 (9.2%)	1,053 (9.3%)	-0.0035
HDHP	1,251 (5.8%)	1,312 (6.1%)	-0.0127	649 (5.5%)	646 (5.5%)	0.0000	622 (5.5%)	626 (5.6%)	-0.0044
ELIXHAUSER INDEX									

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 Days			Clopidogrel : Prasugrel (1:1 PS Match) 30 Days			Ticagrelor : Prasugrel (1:1 PS Match) 30 Days		
Variable	**Clopidogrel N = 21,549**	**Ticagrelor N = 21,549**	**SDs**	**Clopidogrel N = 11,776**	**Prasugrel N = 11,776**	**SDs**	**Ticagrelor N = 11,263**	**Prasugrel N = 11,263**	**SDs**
Category 0	6,627 (30.8%)	6,781 (31.5%)	-0.0151	3,621 (30.7%)	3,612 (30.7%)	0.0000	3,543 (31.5%)	3,481 (30.9%)	0.0130
Category 1	5,770 (26.8%)	5,764 (26.7%)	0.0023	3,788 (32.2%)	3,669 (31.2%)	0.0215	3,445 (30.6%)	3,430 (30.5%)	0.0022
Category 2	1,600 (7.4%)	1,612 (7.5%)	-0.0038	693 (5.9%)	764 (6.5%)	-0.0249	721 (6.4%)	744 (6.6%)	-0.0081
Category 3	4,474 (20.8%)	4,375 (20.3%)	0.0124	2,438 (20.7%)	2,448 (20.8%)	-0.0025	2,308 (20.5%)	2,356 (20.9%)	-0.0099
Category 4	3,078 (14.3%)	3,017 (14%)	0.0086	1,236 (10.5%)	1,283 (10.9%)	-0.0129	1,246 (11.1%)	1,252 (11.1%)	0.0000
BLEEDING RISK									
High Bleeding Risk	8,448 (39.2%)	8,471 (39.3%)	-0.0020	4,150 (35.2%)	4,290 (36.4%)	-0.0250	4,083 (36.3%)	4,155 (36.9%)	-0.0125
MEDICATION HISTORY									
Anti-diabetics									
Antidiabetics (Miscellaneous)	3,687 (17.1%)	3,779 (17.5%)	-0.0106	1,871 (15.9%)	2,029 (17.2%)	-0.0350	1,879 (16.7%)	1,949 (17.3%)	-0.0160
Meglitinide	62 (0.3%)	55 (0.3%)	0.0000	22 (0.2%)	27 (0.2%)	0.0000	20 (0.2%)	26 (0.2%)	0.0000
SGLT inhibitors	469 (2.2%)	511 (2.4%)	-0.0133	182 (1.5%)	219 (1.9%)	-0.0309	210 (1.9%)	217 (1.9%)	0.0000
Sulfnylureas	1,501 (7%)	1,525 (7.1%)	-0.0039	741 (6.3%)	775 (6.6%)	-0.0122	736 (6.5%)	755 (6.7%)	-0.0081
TZDs	250 (1.2%)	245 (1.1%)	0.0094	124 (1.1%)	141 (1.2%)	-0.0094	132 (1.2%)	132 (1.2%)	0.0000
Anti-hypertensive									
ACE Inhibitors	4,837 (22.4%)	4,895 (22.7%)	-0.0072	2,548 (21.6%)	2,681 (22.8%)	-0.0289	2,468 (21.9%)	2,561 (22.7%)	-0.0192
Beta Blockers	6,421 (29.8%)	6,430 (29.8%)	0.0000	3,444 (29.2%)	3,546 (30.1%)	-0.0197	3,298 (29.3%)	3,376 (30%)	-0.0153
Calcium Channel Blockers	3,795 (17.6%)	3,928 (18.2%)	-0.0157	1,682 (14.3%)	1,871 (15.9%)	-0.0447	1,751 (15.5%)	1,815 (16.1%)	-0.0165
ARBs	3,738 (17.3%)	3,835 (17.8%)	-0.0131	1,927 (16.4%)	1,967 (16.7%)	-0.0081	1,862 (16.5%)	1,901 (16.9%)	-0.0107
Diuretics									
Loop Diuretics	1,241 (5.8%)	1,163 (5.4%)	0.0174	492 (4.2%)	559 (4.7%)	-0.0242	538 (4.8%)	530 (4.7%)	0.0047
Potassium Sparing Diuretics	630 (2.9%)	619 (2.9%)	0.0000	329 (2.8%)	338 (2.9%)	-0.0060	317 (2.8%)	317 (2.8%)	0.0000
Thiazide Diuretics	1,461 (6.8%)	1,503 (7%)	-0.0079	707 (6%)	777 (6.6%)	-0.0247	720 (6.4%)	748 (6.6%)	-0.0081
Other Medications									
Anti-Platelets	2,144 (9.9%)	2,085 (9.7%)	0.0067	1,227 (10.4%)	1,294 (11%)	-0.0194	1,186 (10.5%)	1,224 (10.9%)	-0.0129

	Clopidogrel : Ticagrelor (1:1 PS Match) 30 Days			Clopidogrel : Prasugrel (1:1 PS Match) 30 Days			Ticagrelor : Prasugrel (1:1 PS Match) 30 Days		
Variable	**Clopidogrel N = 21,549**	**Ticagrelor N = 21,549**	**SDs**	**Clopidogrel N = 11,776**	**Prasugrel N = 11,776**	**SDs**	**Ticagrelor N = 11,263**	**Prasugrel N = 11,263**	**SDs**
Anti-Arrhythmics	176 (0.8%)	156 (0.7%)	0.0116	81 (0.7%)	89 (0.8%)	-0.0116	82 (0.7%)	81 (0.7%)	0.0000
Anti-Hyperlipidimics	9,164 (42.5%)	9,354 (43.4%)	-0.0182	5,044 (42.8%)	5,221 (44.3%)	-0.0303	4,844 (43%)	4,986 (44.3%)	-0.0262
Anti-Depressants	3,594 (16.7%)	3,680 (17.1%)	-0.0107	1,860 (15.8%)	1,942 (16.5%)	-0.0190	1,803 (16%)	1,881 (16.7%)	-0.0189
Estrogens	319 (1.5%)	348 (1.6%)	-0.0081	187 (1.6%)	204 (1.7%)	-0.0079	175 (1.6%)	196 (1.7%)	-0.0079
PPIs	3,951 (18.3%)	4,020 (18.7%)	-0.0103	2,045 (17.4%)	2,155 (18.3%)	-0.0235	1,963 (17.4%)	2,084 (18.5%)	-0.0287
H2RAs	594 (2.8%)	608 (2.8%)	0.0000	261 (2.2%)	266 (2.3%)	-0.0067	235 (2.1%)	259 (2.3%)	-0.0136

Acronyms: PS: propensity score, EPO: exclusive provider organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: Sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 5. 4 Demographics and Clinical Characteristics of Clopidogrel, Prasugrel, and Ticagrelor Users after Propensity Score Matching at 180 Days

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 Days			Clopidogrel : Prasugrel (1:1 PS Match) 180 Days			Ticagrelor : Prasugrel (1:1 PS Match) 180 Days		
Variable	**Clopidogrel N = 16,880**	**Ticagrelor N = 16,880**	**SDs**	**Clopidogrel N = 9,615**	**Prasugrel N = 9,615**	**SDs**	**Ticagrelor N = 9,130**	**Prasugrel N = 9,130**	**SDs**
AGE CATEGORY									
18-44 Years	1,155 (6.8%)	1,238 (7.3%)	-0.0195	752 (7.8%)	781 (8.1%)	-0.0111	701 (7.7%)	757 (8.3%)	-0.0221
45-64 Years	11,972 (70.9%)	11,965 (70.9%)	0.0000	7,391 (76.9%)	7,387 (76.8%)	0.0024	6,955 (76.2%)	6,948 (76.1%)	0.0023
65-84 Years	3,420 (20.3%)	3,386 (20.1%)	0.0050	1,437 (14.9%)	1,411 (14.7%)	0.0056	1,440 (15.8%)	1,392 (15.2%)	0.0166
85 years & Above	333 (2%)	291 (1.7%)	0.0223	35 (0.4%)	36 (0.4%)	0.0000	34 (0.4%)	33 (0.4%)	0.0000
SEX									
Male	12,536 (74.3%)	12,516 (74.1%)	0.0046	7,594 (79%)	7,511 (78.1%)	0.0219	7,132 (78.1%)	7,110 (77.9%)	0.0048
Female	4,344 (25.7%)	4,364 (25.9%)	-0.0046	2,021 (21%)	2,104 (21.9%)	-0.0219	1,998 (21.9%)	2,020 (22.1%)	-0.0048
REGION									
Northeast	3,477 (20.6%)	3,459 (20.5%)	0.0025	1,625 (16.9%)	1,596 (16.6%)	0.0080	1,538 (16.8%)	1,536 (16.8%)	0.0000
North Central	4,520 (26.8%)	4,413 (26.1%)	0.0159	2,152 (22.4%)	2,120 (22%)	0.0096	2,070 (22.7%)	2,067 (22.6%)	0.0024
South	7,029 (41.6%)	7,140 (42.3%)	-0.0142	4,570 (47.5%)	4,637 (48.2%)	-0.0140	4,396 (48.1%)	4,340 (47.5%)	0.0120
West	1,758 (10.4%)	1,759 (10.4%)	0.0000	1,172 (12.2%)	1,157 (12%)	0.0061	1,038 (11.4%)	1,090 (11.9%)	-0.0156
Other	96 (0.6%)	109 (0.6%)	0.0000	96 (1%)	105 (1.1%)	-0.0098	88 (1%)	97 (1.1%)	-0.0098
PLAN TYPE									
Comprehensive	1,906 (11.3%)	1,820 (10.8%)	0.0159	1,043 (10.8%)	996 (10.4%)	0.0130	937 (10.3%)	955 (10.5%)	-0.0066
EPO	133 (0.8%)	143 (0.8%)	0.0000	78 (0.8%)	82 (0.9%)	-0.0109	70 (0.8%)	77 (0.8%)	0.0000
HMO	1,608 (9.5%)	1,648 (9.8%)	-0.0102	849 (8.8%)	880 (9.2%)	-0.0140	845 (9.3%)	853 (9.3%)	0.0000
POS	998 (5.9%)	1,066 (6.3%)	-0.0167	607 (6.3%)	609 (6.3%)	0.0000	576 (6.3%)	583 (6.4%)	-0.0041
PPO	9,414 (55.8%)	9,156 (54.2%)	0.0322	5,510 (57.3%)	5,539 (57.6%)	-0.0061	5,231 (57.3%)	5,194 (56.9%)	0.0081
POS with capitation	189 (1.1%)	199 (1.2%)	-0.0094	55 (0.6%)	63 (0.7%)	-0.0124	66 (0.7%)	60 (0.7%)	0.0000
CDHP	1,682 (10%)	1,813 (10.7%)	-0.0230	977 (10.2%)	941 (9.8%)	0.0133	918 (10.1%)	924 (10.1%)	0.0000
HDHP	950 (5.6%)	1,035 (6.1%)	-0.0213	496 (5.2%)	505 (5.3%)	-0.0045	487 (5.3%)	484 (5.3%)	0.0000

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 Days			Clopidogrel : Prasugrel (1:1 PS Match) 180 Days			Ticagrelor : Prasugrel (1:1 PS Match) 180 Days		
Variable	**Clopidogrel N = 16,880**	**Ticagrelor N = 16,880**	**SDs**	**Clopidogrel N = 9,615**	**Prasugrel N = 9,615**	**SDs**	**Ticagrelor N = 9,130**	**Prasugrel N = 9,130**	**SDs**
ELIXHAUSER INDEX									
Category 0	5,255 (31.1%)	5,322 (31.5%)	-0.0086	3,005 (31.3%)	2,952 (30.7%)	0.0130	2,852 (31.2%)	2,807 (30.7%)	0.0108
Category 1	4,720 (28%)	4,641 (27.5%)	0.0112	3,166 (32.9%)	3,127 (32.5%)	0.0085	2,915 (31.9%)	2,894 (31.7%)	0.0043
Category 2	1,245 (7.4%)	1,258 (7.5%)	-0.0038	563 (5.9%)	603 (6.3%)	-0.0167	574 (6.3%)	584 (6.4%)	-0.0041
Category 3	3,394 (20.1%)	3,415 (20.2%)	-0.0025	1,920 (20%)	1,966 (20.4%)	-0.0100	1,830 (20%)	1,899 (20.8%)	-0.0199
Category 4	2,266 (13.4%)	2,244 (13.3%)	0.0029	961 (10%)	967 (10.1%)	-0.0033	959 (10.5%)	946 (10.4%)	0.0033
BLEEDING RISK									
High Bleeding Risk	6,448 (38.2%)	6,450 (38.2%)	0.0000	3,321 (34.5%)	3,427 (35.6%)	-0.0231	3,244 (35.5%)	3,319 (36.4%)	-0.0188
MEDICATION HISTORY									
Anti-diabetics									
Antidiabetics (Miscellaneous)	2,811 (16.7%)	2,905 (17.2%)	-0.0133	1,510 (15.7%)	1,599 (16.6%)	-0.0245	1,457 (16%)	1,542 (16.9%)	-0.0243
Meglitinide	41 (0.2%)	40 (0.2%)	0.0000	19 (0.2%)	22 (0.2%)	0.0000	21 (0.2%)	21 (0.2%)	0.0000
SGLT inhibitors	358 (2.1%)	367 (2.2%)	-0.0069	141 (1.5%)	169 (1.8%)	-0.0236	163 (1.8%)	170 (1.9%)	-0.0074
Sulfnylureas	1,136 (6.7%)	1,161 (6.9%)	-0.0079	597 (6.2%)	612 (6.4%)	-0.0082	572 (6.3%)	592 (6.5%)	-0.0082
TZDs	191 (1.1%)	185 (1.1%)	0.0000	108 (1.1%)	113 (1.2%)	-0.0094	98 (1.1%)	115 (1.3%)	-0.0184
Anti-hypertensive									
ACE Inhibitors	3,699 (21.9%)	3,770 (22.3%)	-0.0096	2,128 (22.1%)	2,158 (22.4%)	-0.0072	1,971 (21.6%)	2,068 (22.7%)	-0.0265
Beta Blockers	5,015 (29.7%)	4,961 (29.4%)	0.0066	2,720 (28.3%)	2,839 (29.5%)	-0.0265	2,632 (28.8%)	2,699 (29.6%)	-0.0176
Calcium Channel Blockers	3,001 (17.8%)	3,037 (18%)	-0.0052	1,404 (14.6%)	1,474 (15.3%)	-0.0196	1,400 (15.3%)	1,432 (15.7%)	-0.0111
ARBs	2,929 (17.4%)	3,052 (18.1%)	-0.0183	1,449 (15.1%)	1,582 (16.5%)	-0.0384	1,469 (16.1%)	1,511 (16.5%)	-0.0108
Diuretics									
Loop Diuretics	903 (5.3%)	876 (5.2%)	0.0045	401 (4.2%)	439 (4.6%)	-0.0195	410 (4.5%)	418 (4.6%)	-0.0048
Potassium Sparing Diuretics	490 (2.9%)	476 (2.8%)	0.0060	274 (2.8%)	276 (2.9%)	-0.0060	256 (2.8%)	257 (2.8%)	0.0000
Thiazide Diuretics	1,093 (6.5%)	1,135 (6.7%)	-0.0081	581 (6%)	611 (6.4%)	-0.0166	538 (5.9%)	596 (6.5%)	-0.0249

	Clopidogrel : Ticagrelor (1:1 PS Match) 180 Days			Clopidogrel : Prasugrel (1:1 PS Match) 180 Days			Ticagrelor : Prasugrel (1:1 PS Match) 180 Days		
Variable	**Clopidogrel N = 16,880**	**Ticagrelor N = 16,880**	**SDs**	**Clopidogrel N = 9,615**	**Prasugrel N = 9,615**	**SDs**	**Ticagrelor N = 9,130**	**Prasugrel N = 9,130**	**SDs**
Other Medications									
Anti-Platelets	1,622 (9.6%)	1,582 (9.4%)	0.0068	919 (9.6%)	981 (10.2%)	-0.0201	925 (10.1%)	923 (10.1%)	0.0000
Anti-Arrhythmics	123 (0.7%)	120 (0.7%)	0.0000	68 (0.7%)	67 (0.7%)	0.0000	63 (0.7%)	64 (0.7%)	0.0000
Anti-Hyperlipidimics	7,130 (42.2%)	7,228 (42.8%)	-0.0121	4,058 (42.2%)	4,206 (43.7%)	-0.0303	3,892 (42.6%)	3,993 (43.7%)	-0.0222
Anti-Depressants	2,782 (16.5%)	2,822 (16.7%)	-0.0054	1,526 (15.9%)	1,571 (16.3%)	-0.0109	1,441 (15.8%)	1,510 (16.5%)	-0.0190
Estrogens	266 (1.6%)	280 (1.7%)	-0.0079	151 (1.6%)	163 (1.7%)	-0.0079	153 (1.7%)	155 (1.7%)	0.0000
PPIs	3,118 (18.5%)	3,161 (18.7%)	-0.0051	1,652 (17.2%)	1,705 (17.7%)	-0.0132	1,555 (17%)	1,602 (17.5%)	-0.0132
H2RAs	484 (2.9%)	469 (2.8%)	0.0060	209 (2.2%)	215 (2.2%)	0.0000	214 (2.3%)	209 (2.3%)	0.0000

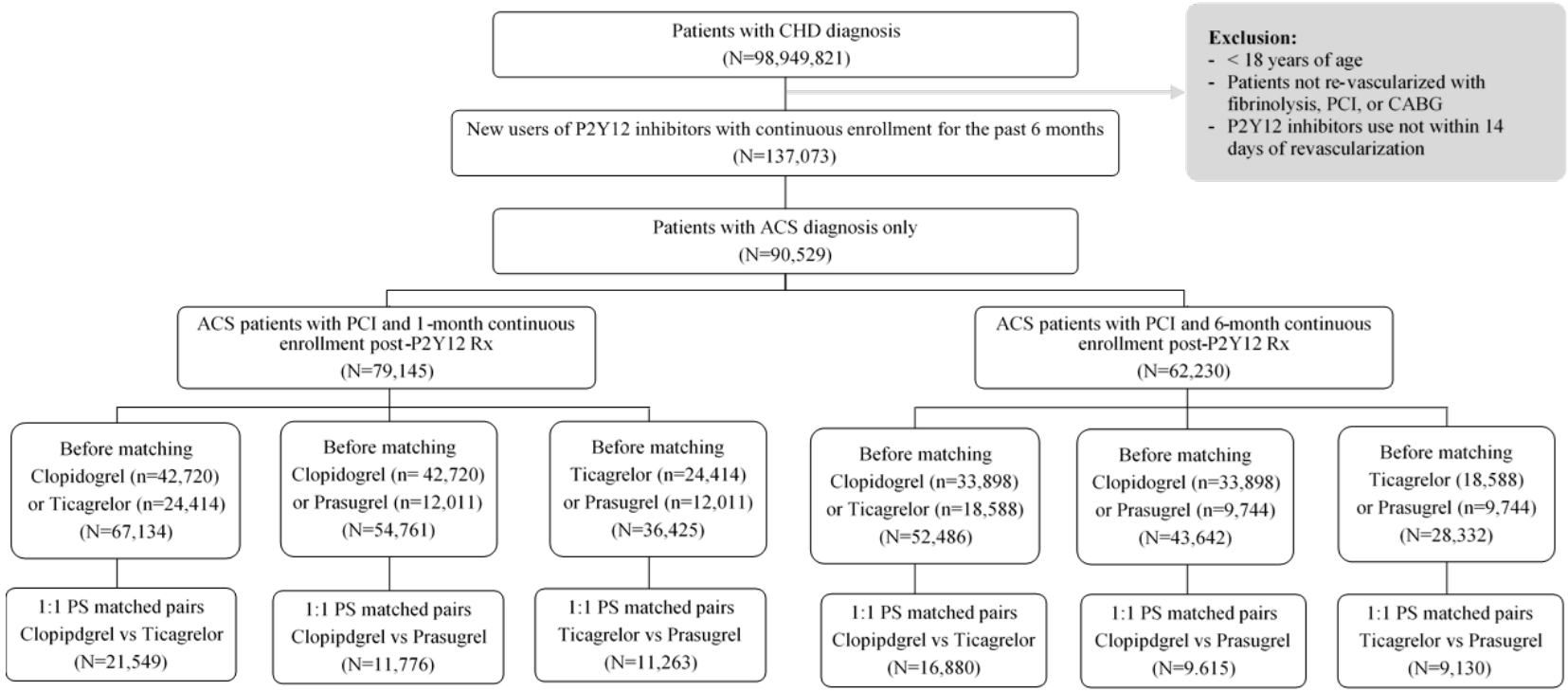
Acronyms: PS: propensity score, EPO: Exclusive Provider Organization, HMO: health maintenance organization, POS: point-of-service, PPO: preferred provider organization, CDHP: consumer-driven health plan, HDHP: high-deductible health plan; STEMI: ST wave elevated myocardial infarction; NSTEMI: Non-ST elevated myocardial infarction; UA: unstable angina; NSAIDs: non-steroidal anti-inflammatory drugs; GLP-1: glucagon-like peptide 1 agonist; DPP-4: dipeptidyl peptidase 4; SGLT: Sodium-glucose co-transporter inhibitors; TZD: thiazolidinediones; PPIs: proton pump inhibitors; H2RA: H2 receptor *blockers*.

Appendix Table 5. 5 Number of Events, Cumulative Incidence, and Absolute Risk Difference for Secondary Safety Outcomes In 1:1 PS-Matched Comparisons

P2Y12 inhibitor	Number of events	Total number of patients	Cumulative Incidence	% Absolute Risk Difference
Gastrointestinal Bleeding				
30 days outcomes PS Matched Comparisons				
Clopidogrel versus Ticagrelor				
Clopidogrel	37	21549	0.001717017	-0.009281173
Ticagrelor	35	21549	0.001624205	
Clopidogrel versus Prasugrel				
Clopidogrel	23	11776	0.001953125	-0.025475543
Prasugrel	20	11776	0.00169837	
Ticagrelor versus Prasugrel				
Ticagrelor	19	11263	0.00168694	0.008878629
Prasugrel	20	11263	0.001775726	
180 days outcomes PS Matched Comparisons				
Clopidogrel versus Ticagrelor				
Clopidogrel	104	16880	0.006161137	-0.148104265
Ticagrelor	79	16880	0.004680095	
Clopidogrel versus Prasugrel				
Clopidogrel	65	9615	0.00676027	-0.124804992
Prasugrel	53	9615	0.00551222	
Ticagrelor versus Prasugrel				
Ticagrelor	41	9130	0.00449069	0.230010953
Prasugrel	62	9130	0.0067908	

Note: *PSMATCH (1:1)*- Propensity score matching (1:1) with nearest-neighbor matching technique without replacement

Appendix Figure 5. 1 Flowchart of Patients' Inclusion



Acronyms: CHD: coronary heart disease**,** PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, ACS: acute coronary syndrome, PS: a propensity score, P2Y12 Rx: prescription of either clopidogrel, prasugrel, or ticagrelor

CHAPTER 6: DISCUSSION

The goal of this dissertation was to examine the prescription pattern, comparative effectiveness, and safety of P2Y12 inhibitors in real-world clinical practice. The three studies conducted for this dissertation present the result of this research work.

In summary, in Study 1, we first described the utilization of P2Y12 inhibitors commonly used in coronary heart disease (CHD) based on important factors outlined under Andersen's behavioral model (ABM) of healthcare use which includes predisposing demographics, enabling, and need variables. We then looked at the prescription pattern of P2Y12 inhibitors following revascularization with fibrinolysis, PCI, and CABG in CHD. We further examined how the prescription patterns of these P2Y12 inhibitors differ in US clinical practice across a number of clinical characteristics that might influence treatment selection. These characteristics include high risk of bleeding and history of stroke or TIA.

Studies 2 and 3 determined the comparative effectiveness and safety of P2Y12 inhibitors specifically in ACS patients undergoing a PCI, respectively. Effectiveness was assessed according to many important clinical factors such as ACS presentation (STEMI and NSTEMI), type of stents (BMS and DES), and gender. Similarly, safety was assessed across a number important factors such as gender, advanced age, and high bleeding risk.

6.1. Summary of Findings

6.1.1. STUDY 1: Prescription Patterns of P2Y12 Inhibitors Following Revascularization in the United States: 2013-2018

This study was conducted using 92,734 and 44,339 patients with a CHD managed with revascularization from CCAE and MDCR data samples, respectively. We discovered that patients with lower age brackets were more likely to have used newer P2Y12 inhibitors compared to clopidogrel. We noted that the use of clopidogrel continued to decrease in the CCAE sample from the year 2013 to 2018 and during the year 2018, ticagrelor became the choice of drug. However, for the MDCR sample, we saw that although decreasing with time, clopidogrel remained the most prescribed drug throughout the study period. However, the use of prasugrel continued to decrease in both of the data samples and its use remained well below the use of the other two drugs. For the technique of revascularization, in the CCAE sample, ticagrelor was again the most prescribed drug in 2018 after a continuous surge in its prescription among the patients managed with PCI, but clopidogrel was the most prescribed drug in patients managed with fibrinolysis and CABG. Nevertheless, clopidogrel was the most used drug regardless of the revascularization technique in the MDCR sample. However, for the patients at high risk of bleeding, history of stroke/TIA, and higher comorbidity index, clopidogrel remained the most utilized drug in both of the samples. For the predictors of drug utilization, we observed the odds of use of ticagrelor over clopidogrel and prasugrel to be increasing over the years. For the type of revascularization, those undergoing CABG compared to PCI were more likely to use clopidogrel compared to ticagrelor for both of the data samples. For the stent type, in both of the samples, we observed higher use of newer P2Y12 inhibitors compared to clopidogrel for those managed with DES

compared to BMS stents. Additionally, we observed higher use of newer P2Y12 inhibitors compared to clopidogrel among the patients presented with STEMI compared to NSTEMI/UA for both of the data samples. Also, among the patients with high bleeding risk and a history of stroke, clopidogrel was most likely to be prescribed compared to newer P2Y12 inhibitors.

6.1.2. STUDY 2: Comparative Effectiveness of P2Y12 Inhibitors for Secondary Prophylaxis in Acute Coronary Syndrome after Percutaneous Coronary Intervention

In this large study, in the first phase, we combined CCAE and MDCR populations (overall sample) and included 79,145 and 62,230 patients to determine the effectiveness across P2Y12 inhibitors over 30 and 180 days, respectively. In the second phase (sensitivity analysis), we studied CCAE and MDCR population samples separately. In this study, the effectiveness was measured as hospitalization due to a composite cardiovascular outcome including recurrent myocardial infarction, unstable angina, recurrent revascularization (Fibrinolysis, PCI, or coronary artery bypass graft (CABG)), stroke (ischemic or hemorrhagic), and heart failure at 30^{th} and 180^{th}-day post PCI.

Overall Sample

In Clopidogrel versus ticagrelor users, in unadjusted comparisons, ticagrelor was associated with an 11% reduced risk of composite cardiovascular outcome compared to clopidogrel in 30 days. However, this effect was not significant after PS matching. Similarly, at 180 days, we observed a 21% risk reduction associated with ticagrelor that was found not different compared to clopidogrel in PS matched comparisons. During the subgroup analyses, we did not see any differences between the groups as per the type

of ACS and stent. However, at 30 days follow up, ticagrelor was associated with a 20% lower risk compared to clopidogrel in the female population which was not different at 180 days. For both follow-up times, there were no differences in both drugs in the male population.

Similarly, in Clopidogrel versus prasugrel users, before matching, in 30 days, compared to clopidogrel, prasugrel was associated with a 25% reduced risk of the composite cardiovascular outcome that was not significantly different in PS matched comparison. Identical to 30 days companion, in 180 days, we observed a 29% reduced risk associated with prasugrel which was not different after PS matching. The results were similar to the primary analysis in all subgroups we studied.

Finally, for Ticagrelor versus prasugrel comparison, prasugrel, compared to ticagrelor (before matching) was associated with a statistically significant 16% and 11% reduced risk of the composite cardiovascular outcome at 30 days and 180 days, respectively. However, there was no difference between the groups in PS matched comparisons in 30 and 180 days similar to the other PS matched comparisons in the study.

Sensitivity Analysis

We observed similar results in the sensitivity analysis for the primary analysis. However, importantly, in the subgroup analysis in the CCAE sample, we observed a 33% lower risk associated with prasugrel compared to clopidogrel in the female population in 30 days. Additionally, ticagrelor was found to be associated with better outcomes compared to prasugrel in females as prasugrel was associated with an 84% higher incidence of the composite cardiovascular outcome at 180 days in the MDCR sample. Also, those who

were managed with BMS stent in the CCAE sample and prescribed with prasugrel were associated with a reduced risk of 43% at 180th day compared to ticagrelor.

6.1.3. STUDY 3: Comparative Safety of P2Y12 Inhibitors for Secondary Prophylaxis in Acute Coronary Syndrome after Percutaneous Coronary Intervention

Similar to Study 2, we conducted this study by combining both CCAE and MDCR sample populations. The primary safety outcome of major bleeding in this study was determined using inpatient discharge codes for intracranial (IC), gastrointestinal (GI), or other serious forms of bleeding as a composite outcome i.e., major bleeding.

For the clopidogrel versus ticagrelor users, before PS matching, ticagrelor was associated with a 33% reduced risk of composite major bleeding outcome compared to clopidogrel in 30 days. However, this effect was not significant after PS matching. Similarly, at 180 days, we observed a 32% risk reduction associated with ticagrelor that was found not different compared to clopidogrel in PS matched comparisons. During the subgroup analyses, we did not see any difference between the groups based on gender, advanced age, or high bleeding risk in 30 days and 180 days. Similarly, for the clopidogrel and prasugrel users, before matching, there was no difference between the groups for major bleeding at both follow-up times. This effect was consistent in PS matched comparisons as there was no difference between the groups in 30 and 180 days. Subgroup analysis showed similar results to the primary analysis.

Additionally, we found no difference between the groups at both of the time points before PS matching for the prasugrel and ticagrelor comparison. We continued to see no difference between the groups after PS matched comparisons in 30 days

outcomes. However, on the 180th day, we observed a significant 44% increased major bleeding risk with prasugrel compared to ticagrelor. During the subgroup analysis, we found that the risk of major bleeding was more pronounced among patients less than 70 years of age as we observed a 64% higher risk of hospitalization with major bleeding associated with prasugrel use compared to ticagrelor in this age group.

We also measured the risk of gastrointestinal bleeding events as a secondary safety outcome. We observed very similar results as observed for the composite major bleeding outcome. Similar to the primary safety outcome, we observed a 51% higher risk associated with prasugrel compared to ticagrelor in 180 days.

6.2. Implications of Findings

The results of the first specific aim in this dissertation concur with the previous findings that the use of ticagrelor is increasing in the US with time. [154,155] As guidelines recommend the use of newer P2Y12 inhibitors for the ACS patients undergoing PCI,[220] channelings away from clopidogrel occurred in our sample, especially in the younger population. This might be the reason why ticagrelor became the most prescribed P2Y12 inhibitor among patients under the age of 65 years and those managed with a PCI.

We also report the increasing use of ticagrelor among patients over 65 years of age; however, throughout the study period (2013-2018), clopidogrel remained the most prescribed P2Y12 inhibitor irrespective of the revascularization technique among patients aged over 65 years. Advanced age has been cited as an increased risk for bleeding (citation) and that could be a reason why we saw increased use of clopidogrel in this age group.

Additionally, in our study, we observed higher use of newer P2Y12 inhibitors with lower comorbidities level as measured by Elixhauser conditions. Our study thus, suggests a selective use of clopidogrel with higher comorbid levels, which is consistent with a previous study that reported higher use of clopidogrel compared to newer P2Y12 inhibitors among patients with a higher Charlson comorbidity index.[179] As higher associated comorbidities are associated with a higher risk of bleeding,[221] higher comorbidity level in our samples was a strong predictor of clopidogrel use. It implies that in our samples, frailer patients were more likely to initiate clopidogrel compared to newer P2Y12 inhibitors.

Also, STEMI presentation was associated with higher use of newer P2Y12 inhibitors in our sample which is consistent with the AHA/ACC guidelines that recommend the use of newer P2Y12 inhibitors over clopidogrel in STEMI patients (citation).

Furthermore, we saw in our sample populations that increased bleeding risk also decreased the likelihood of newer P2Y12 inhibitors. A higher trend of clopidogrel compared to newer P2Y12 inhibitors may be a default choice because of the proven higher risk of bleeding in the PLATO and TRITON TIMI 38 trials with newer agents. This is possible that physicians were more cautious to prescribe newer P2Y12 inhibitors because of the bleeding risk associated with these.

Overall, we observed many factors which predicted the choice of one P2Y12 inhibitor over the other. Although we observed a clear reflection of AHA/ACC guidelines in the clinical practice in our samples, we also observed the unintended use of prasugrel among the patients with a history of stroke/TIA that is contraindicated. Also, despite

lower than clopidogrel, we continued to see the use of newer P2Y12 inhibitors in high bleeding risk as well.

This behavior in drug use may represent how the use of P2Y12 inhibitors can differ as per the clinical characteristics which may have important policy implications for appropriate prescribing such as to avoid the use of prasugrel wherever it is contraindicated/unnecessary. We also observed some discrepancies in the prescription fills with newer P2Y12 inhibitors as per the plan the patients were enrolled in. This could be due to the reason that some plans were more generous than others to cover expensive medications. These patterns may represent how insurance plans can have an impact on disease management. This information can help policymakers in better disease management by studying the factors involved in the discrepancies of P2Y12 use in different plans. Additionally, we presented how newer P2Y12 inhibitors penetrated the US market and the factor associated with their use. This information may provide important information to stakeholders interested in the management of coronary heart disease.

As in our samples, we observed the increasing use of ticagrelor with time in the US, it is imperative to study the effectiveness and safety of newer agents to maintain a balance because of associated bleeding risk with their use. Keeping all these changing trends of P2Y12 agents in the US in mind, we designed our specific aim 2 and 3 to assess the safety and effectiveness across P2Y12 inhibitors. We studied the effectiveness and safety of P2Y12 inhibitors in different arrays of clinical characteristics. First and foremost, we present the most current evidence related to effectiveness and safety using a sample that represents a broader real-world US population. Before this

study the results were primarily derived from RCTs or observational studies that were not generalizable to a broader US population, hence we address this research gap.

Additionally, we studied several clinical parameters that may impact the effectiveness and safety across different P2Y12 inhibitors. We present the evidence of effectiveness across the different spectrum of ACS presentations (i.e., STEMI and NSTEMI/UA), type of stent (i.e., BMS and DES), and sex. These clinical determinants are believed to be associated with differential risk for re-infarction that has significant clinical and policy implications. Moreover, we studied the safety across different P2Y12 inhibitors in different clinical characteristics including sex, advanced age, and high bleeding risk (defined as (i) High-risk comorbidities in the past six months (i.e. diabetes mellitus, anemia, chronic kidney disease (CKD), and low body weight (LBW)) (ii) history of prior major bleeding (i.e., intracranial (IC), gastrointestinal (GI) and any other major bleeding)), and (iii) concomitant use of high-risk medications (i.e., oral anticoagulants, Rx NSAIDs, or steroids)). These clinical characteristics are very important to find a balance between higher platelet inhibition and bleeding risk while using newer P2Y12 inhibitors. The results of this dissertation will help clinicians make better decisions in the management of ACS patients undergoing a PCI.

6.3. Important Limitations and Future Directions

Both findings and limitations of this study suggest some future directions. One of the limitations of this study is that we couldn't study the effect of aspirin on our patient population. Because aspirin is available as an over-the-counter drug in the US and MarketScan data doesn't have this information, we couldn't see if patients were using aspirin as directed. Aspirin is an integral part of DAPT that is given along with a P2Y12

inhibitor. This makes it necessary to study this while comparing the effectiveness and safety across P2Y12 inhibitors.

Additionally, in the PLATO trial that studied the efficacy and safety of ticagrelor and clopidogrel, a significant interaction was found with the region which indicated no benefit with ticagrelor in the North American population. Researchers spotted the high dose aspirin use in Americans compared to the rest of the world as one of the possible reasons for no difference between ticagrelor and clopidogrel. [124,125] None of the observational studies since then have looked at the effect of dose of Aspirin on the comparative effectiveness of P2Y12 inhibitors in the US which we proposed to study using a registry or electronic health record (EHR). The finding of this proposed study has the potential to impact the current clinical practice as clopidogrel is available as a generic medication in the US and is much cheaper than clopidogrel. Such a study will inform the decision-makers whether to continue the use of ticagrelor which is extensively used in the US population since its approval.

Moreover, the MarketScan database doesn't have information related to patients' lab values, vital signs, and other rich information related to patient behavior such as smoking, drinking habits, and socioeconomic status. These are important factors that should be assessed to measure patients' cardiovascular health. Thus, we recommend using EHR data to conduct a similar study by adjusting for these factors. The information from EHR may address several other limitations of this study. For example, the MarketScan database does not possess the information related to the confirmatory tests for an ACS event to make a definite diagnosis. Myocardial infarction is assessed mainly based on the EKG reports along with cardiac-specific enzyme tests such as Troponin C

and Troponin I. The rise of these cardiac-specific enzymes in blood within few hours confirms the diagnosis of an MI attack assisted with EKG interpretations. Moreover, the severity of the attacks can be assessed using this information. Using cardiologists' notes along with other diagnostic criteria can provide much richer information to assess the prognosis. The severity of the clinical course of the disease may bring a change in the course of action with a need for greater platelet aggregation inhibition, which we proposed to study along with the comparative effectiveness of P2Y12 inhibitors.

Furthermore, in our study, we didn't have access to the information on whether the PCI conducted was primary or elective in nature. Based on the information we had available from MarketScan data, our study population might be undergoing a primary PCI as we coded our patients to be the incident users by eliminating the use of prior P2Y12 inhibitors. However, we did not have any other information that can assess to confirm whether the PCI was primary or elective. Intervention cardiologists while performing a PCI may provide some important information (that is not captured by claims data) in the patients' chart whether the PCI conducted is elective or primary. This information is crucial and needs to be considered (if available) while studying these drugs as the guidelines for the management change with the mode of PCI. As elective PCI is recommended for stable ischemic heart disease (SIHD), the course of P2Y12 inhibitors for recurrent cardiovascular events differs compared to ACS patients. For example, among patients with SIHD, clopidogrel is the only drug that has been given the class I recommendation by ACC/AHA guidelines.[40] Thus, we suggest studying these medications by including this information from electronic health records or registry data.

Additionally, we didn't have the information about the time-sensitive treatments while performing a PCI. While performing a PCI, the periprocedural use of Glycoprotein IIb/II3b inhibitors (i.e., abciximab, eptifibatide, and tirofiban), heparins, bivalirudin, and cangrelor has been indicated to prevent thrombotic adverse events,[222] which we could not assess given the limitation of the MarketScan database. Also, adding these time-sensitive treatments may be studied while assessing the comparative effectiveness of P2Y12 inhibitors by future researchers.

Also, as we used incident user design by eliminating any use of P2Y12 inhibitors before PCI, we couldn't assess the effect of a loading dose of P2Y12 inhibitors before the PCI (pretreatment phase). Pretreatment with P2Y12 inhibitors has been shown to have a protective effect against adverse cardiovascular events[223] in RCTs that might affect the effectiveness and safety with further treatment of P2Y12 inhibitors. As we based our analysis on claims data, this time-sensitive granular information was not available in MarketScan data which may be studied using EHR data. We recommend conducting an observational study assessing the comparative effectiveness of P2Y12 inhibitors pretreated with a loading dose compared to those not given loading dose as the effect of loading dose on the future cardiovascular outcome is highly inconsistent.[224-226]

Also, the MarketScan database doesn't have information about the generation of DES used while performing a PCI. Although we could differentiate between DES and BMS, we couldn't differentiate first and second-generation DES from each other. As second-generation DES were associated with a lower tendency to cause stent thrombosis compared to first-generation DES in a meta-analysis,[227] the comparative effectiveness of

P2Y12 inhibitors may be studied based on the generation of DES used by future researchers.

Importantly, a genetic variation in the CYP2C19 enzyme has been linked with a major adverse cardiac outcome among patients undergoing a PCI. For this reason, FDA has issued a black box warning against the use of clopidogrel among the poor metabolizers and has suggested the use of alternative P2Y12 inhibitors.[228] Given that genotype testing is performed, less costly clopidogrel may have the potential to become a preferred treatment among the candidates of PCI who are not poor metabolizers. However, MarketScan data does not have such information that limited us on studying these. Future researchers may test the comparative effectiveness and safety of genotype-guided clopidogrel treatment with newer P2Y12 inhibitors.

Finally, the MarketScan claims data may not be generalizable to patients with age more than 65 years as this data contains information only about the Medicare Supplement population. Medicare Supplement population avail their insurance coverage from their employers which may represent only the richer and healthier population that may not be reflective of the broader US population with age more than 65 years. As increasing age is associated with increased cardiovascular morbidity and bleeding risk, the effect of P2Y12 inhibitors may also differ as newer P2Y12 inhibitors in RCTs are associated with bleeding risk. Thus, it is imperative to study the effect of these drugs in this age segment and we suggest a similar study to be conducted using the traditional Medicare data to assess the effectiveness and safety of P2Y12 inhibitors to assess the clinical outcomes.

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