PASS Information

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Research question and objectives	Primary objective: To compare net adverse clinical events (NACE) up to one year post discharge from the index hospitalization in ACS patients with no history of TIA or stroke, managed with PCI, and treated with prasugrel vs. ticagrelor Secondary objectives: To compare clinical and economic outcomes, and treatment patterns up to one year post discharge from the index hospitalization in ACS patients with no history of TIA or stroke, managed with PCI, and treated with prasugrel vs. ticagrelor
Country of study	US
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Marketing Authorisation Holder

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2. List of Abbreviations

Term	Definition
ACEi	Angiotensin converting-enzyme inhibitor
ACS	Acute Coronary Syndrome
ACS-PCI	ACS managed with PCI
ADP	Adenosine diphosphate
ADP-ri	Adenosine diphosphate receptor inhibitor
AE	Adverse event
ANCOVA	Analysis of covariance
AR	Adverse reaction
ARB	Angiotensin II receptor blocker
ARC	Academic Research Consortium
BMS	Bare metal stent
CABG	Coronary artery bypass graft
CBC	Complete blood count
CCU	Coronary Care Unit, Cardiac Care Unit, or Critical Care Unit
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CLT	Central Limit Theorem
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CT	Computed tomography
CV	Cardiovascular
CXR	Chest x-ray
DES	Drug eluting stent
DSI	Daiichi Sankyo Incorporated

ECG	Electrocardiogram
ED	Emergency department
EMR	Electronic medical record
ERB	Ethical Review Board
FDA	Food and drug administration
FDAMA 114	FDA Modernization Act section 114
GLM	Generalized linear model
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICD-9 CM	International Classification of Disease-9th Ed. Clinically Modified
ICU	Intensive care unit
IRB	Institutional review board
Lilly	Eli Lilly and Company
LOS	Length of stay
MACE	Major Adverse Cardiovascular Event(s)
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NACE	Net Adverse Clinical Events
NCPDP	National Council for Prescription Drug Programs
NSAID	Nonsteroidal anti-inflammatory drug
NSTEMI	Non-ST-segment elevation myocardial infarction
OAP	Oral antiplatelet
OLS	Ordinary Least Squares
PCI	Percutaneous coronary intervention
PFT	Pulmonary function tests
PLATO	Study of Platelet Inhibition and Patient Outcomes
PPI	Proton pump inhibitors
PRBC	Packed red blood cells

RCT	Randomized clinical trial
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Standard deviation
SSDI	Social security death index
STEMI	ST-segment elevation myocardial infarction
TBD	To be determined
TIA	Transient Ischemic Attack
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38
UA	Unstable angina
WB	Whole blood

3. List of Definitions

Acute Coronary Syndrome (ACS)
A cluster of events with coronary artery disease complicated by an acute intracoronary thrombus including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA).

ACS-PCI Hospitalization
An inpatient admission with primary or secondary diagnosis codes for ACS and procedure codes for a percutaneous coronary intervention (PCI).

Adherence
Adherence is defined as the consistency and accuracy with which a patient follows a recommended medical regimen. Post-discharge adherence will be estimated for the index therapy and by class (adenosine diphosphate receptor inhibitors of interest) using the proportion of days covered (PDC) over the 12 months following initiation of the index therapy, in agreement with guideline recommendations for this class of drugs.

Adenosine diphosphate receptor inhibitor (ADP-ri)
ADP-ri medications of interest in this study are clopidogrel, prasugrel, and ticagrelor.

Adverse Event
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

All-cause Mortality
Death specified as discharge status on an inpatient facility claim or by a date of death in the Social Security Death Index, regardless of cause.

Baseline
The primary baseline period of interest is 12 months prior to index hospitalization admission. However, this period may be limited to 6 months to increase sample size if necessary. As a sensitivity analysis, additional history, if available, may be examined over the three years prior to the index hospitalization (going as far back as 31 July 2008) for patients included in the cohort to assess pre-admission characteristics such as history of TIA or stroke.

Bleeding
Bleeding will be identified by ICD-9 diagnosis and/or procedure codes for bleeds or blood transfusions during medical encounters. Major/severe bleeding events will be defined as the presence of either 1) ICD-9 diagnosis and/or procedure codes for bleeding and ≥3 units of transfusions within the same inpatient hospitalization, or 2) no bleeding diagnosis code and ≥4 units of transfusion within 2 days, or 3) ICD-9 codes for intracranial hemorrhage, or 4) ICD-9

and/or procedure codes for blood transfusions within an inpatient hospitalization followed by death for any reason within 72 hours.[1]

Cardiovascular (CV) events
Medical events related to thrombi or emboli within the cardiovascular system. ICD-9 codes and/procedure codes for CV events will be defined in the SAP.

Concomitant medication
CV and non-CV medications that have an overlapping days supply with the index therapy (prasugrel or ticagrelor), stratified as chronic (≥1 refill after initial fill within 60 days) or acute.

Discontinuation
Discontinuation will be defined by a gap of 30 days or more in prescription fills. Discontinuation will be examined for the index therapy and by class (ADP-ris of interest).

Dosing
Dose of the index drug prescription fill will be estimated using quantity of pills, drug strength, and days of drug supplied.

Dyspnea
An episode of dyspnea will be identified with a primary or secondary diagnosis code of dyspnea.

Follow-up
Days from the index hospitalization discharge date to the earliest date of death, loss of data stability, or end of follow-up (one year maximum after discharge date of index hospitalization).

Health Care Resource Utilization

Medical Encounters

Medical encounters will be classified into the following categories of health care services:

- *Inpatient admissions* will be defined as hospitalizations during the study period.
- *Emergency department visits* will be stratified as visits to emergency treatment centers or hospital emergency rooms that do and do not result in an inpatient admission during the study period.
- *Ambulatory visits* will be defined as office visits to primary or specialty care providers, urgent care clinics, outpatient hospitals, and other outpatient settings including laboratory, radiology, and specialty care during the study period.
- *Pharmacy fills* will be defined as outpatient filled prescriptions (including initial fills and refills) during the study period.

All-cause Medical Encounters

Medical encounters associated with primary or secondary diagnosis and procedure codes for all services during the study period.

Disease- and Procedure-related Medical Encounters

Medical encounters associated with the diagnosis and treatment of dyspnea, bleeding, CV events (e.g., MI, revascularization, stroke, unstable angina, congestive heart failure, and bradyarrhythmia; to be further defined in the SAP)

Health Care Charges

All-cause Medical and Pharmacy Charges

Health care charges will be defined as the combined health plan and patient charge amounts for all services, including inpatient admissions, emergency department visits, ambulatory care visits (e.g. outpatient hospital care, physician services, and other ancillary services like physical therapy, laboratory and radiology services), and outpatient pharmacy fills during the study period. Total charges will be defined as the sum of all medical and pharmacy charges.

Disease- and Procedure-Related Medical Charges

The health plan and patient paid amounts for medical encounters associated with the diagnosis and treatment of dyspnea, bleeding, CV events (e.g., MI, revascularization, stroke, unstable angina, congestive heart failure, and bradyarrhythmia; to be further defined in the SAP).

Disease-Related Pharmacy Charges

The health plan and patient paid amounts of outpatient pharmaceuticals for treating CV events and their associated sequelae including, but not limited to, antiplatelet agents and anticoagulants.

Index Admission Date

The index admission date will be defined as the admission date of the index hospitalization.

Index Therapy

The first fill for prasugrel or ticagrelor within 30 days after discharge from the index hospitalization.

Index Therapy Fill Date

The date of the first fill for the index therapy post-index hospitalization discharge, including the date of index hospitalization discharge.

Index Hospitalization

First hospitalization during the selection window with primary or secondary ACS diagnosis codes, PCI procedure codes, and at least one claim for prasugrel or ticagrelor within 30 days post-discharge. For subjects with multiple hospitalizations during the selection window, the first such hospitalization will be selected as the index hospitalization to maximize the available follow-up.

Loss of Data Stability

Loss of data stability will be defined as the absence of claims for any cause (except death) during a particular study period (e.g., patients included in the study cohort will be required to have a claim for any physician visit within 90 days of the index date to ensure data stability of medical claims). Data stability will be used as a proxy for continuous enrolment, as health plan enrolment is not captured in this database.

Major Adverse Cardiovascular Event(s) (MACE)
MACE is a composite endpoint of cardiovascular events that has been widely used in the CV literature[2] to characterize the overall efficacy or effectiveness of treatment. In this study, MACE will be defined as a composite measure of all-cause mortality, revascularization (PCI or coronary artery bypass graft [CABG]) post discharge, or rehospitalization associated with myocardial infarction (MI), unstable angina (UA), transient ischemic attack (TIA), stroke, or congestive heart failure (CHF). Only primary codes for MI, UA, TIA, or stroke will be used where primary or secondary codes will be used for CHF.

Myocardial infarction
In this study, the endpoint or diagnosis of MI will include both ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI). MI will be defined using primary ICD-9 codes for clinical endpoints, and primary or secondary diagnosis codes for the index ACS event. Diagnosis codes will be used to distinguish between STEMI and NSTEMI.

Net Adverse Clinical Event(s) (NACE)
In this study, NACE will be defined as the composite measure of MACE (as defined above) or rehospitalization for bleeding. Rehospitalization for bleeding will be defined as an inpatient admission post-discharge from the index hospitalization, with a primary or secondary bleeding ICD-9 diagnosis or transfusion (defined as administration of one or more units of whole blood [WB] or packed red blood cells [PRBC]) procedural codes.

Overall treatment duration
The number of days between the first fill and the run-out date of last fill for the index therapy during follow-up.

Persistence
Persistence estimates the amount of time that subjects continuously filled prescriptions before a 30-day gap in therapy or the end of the study period.

Prescription Pill burden
Daily pill burden (number of pills taken daily) will be used as a proxy for polypharmacy and to reflect contact with medical system.

Prescriber specialty
The physician specialty on the first pharmacy claim for the post-discharge index therapy will be identified.

Quan-Charlson Comorbidity Index
The Quan-Charlson comorbidity index is an update of the Charlson comorbidity score and serves as a proxy for the cumulative likelihood of one-year mortality or the burden of comorbidity.

Rehospitalization
Any inpatient admission during the study follow up period (i.e., after index hospitalization).

Revascularization
In this study, the definition of revascularization is limited to the performance of coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI).

Selection Window
Timeframe for identifying the index hospitalization: 01 August 2011 to 31 May 2013.

Stent thrombosis
As adapted from the Academic Research Consortium [ARC] definition of probable stent thrombosis, in this study, stent thrombosis will be defined as death or a myocardial infarction within 30 days of stenting, as there are no codes specifically related to stent thrombosis available..[3]

Study Index date
The first day of discharge from the index ACS-PCI hospitalization will be considered the index date for this study.

Switching
Switching will be defined by presence of a prescription for an alternative ADP-ri, not the post-discharge index therapy.

Time to first index medication dispensing/fill
The time to first index therapy fill post-discharge will be calculated by subtracting the index hospitalization discharge date from the index therapy fill date, inclusive of the index hospitalization discharge date.

3. Responsible Parties

Hsiao Lieu, MD, Sr. Medical Director, Eli Lilly and Company

4. Abstract

- Title: Post-discharge Clinical and Economic Outcomes Among Patients with ACS Managed with PCI and Treated with Prasugrel vs. Ticagrelor

- Rationale and background: While the results from the TRITON-TIMI 38 and PLATO trials suggest a superior anti-thrombotic efficacy of prasugrel or ticagrelor, respectively, in combination with aspirin over clopidogrel plus ASA, there is a lack of head-to-head randomized clinical trials (RCT)s or long-term observational data that directly compares clinical and economic outcomes in ACS-PCI patients between prasugrel and ticagrelor post discharge from a ACS-PCI hospitalization. As such, an observational retrospective database analysis will help to fill in this important gap in the literature.

- Research Objectives: The primary study objective is to compare net adverse clinical events (NACE) up to 1 year post discharge from an index ACS-PCI hospitalization in patients treated with prasugrel vs. ticagrelor. Secondary objectives are to compare economic and other clinical outcomes, and treatment patterns up to 1 year post discharge from an index ACS-PCI hospitalization in patients treated with prasugrel vs. ticagrelor.

- Study design: Retrospective cohort study

- Population: The primary study population will be adults with ACS managed with PCI and no history of TIA or stroke, and treated with prasugrel or ticagrelor. The following subgroups of interest will be examined: 1) adults with ACS-PCI with no prior TIA or stroke excluding patients ≥75 years of age without diabetes or prior MI; and (2) other subgroups of the primary population stratified by important characteristics (age, gender, comorbidities of interest) to be finalized in the SAP.

- Variables: The primary dependent variable will be net adverse clinical events (NACE) up to one year. Secondary dependent variables will include resource utilization and other clinical outcomes; healthcare charges; and treatment patterns at 30 days, 6 months, and one year post discharge from the index hospitalization. Study timeframes to be finalized in the SAP. The primary independent variable will be treatment cohort (prasugrel vs. ticagrelor) and other independent variables (covariates) will include baseline demographic and clinical characteristics, and baseline treatment and resource utilization

- Data sources: ProMetis Lx® Database

- Study size: Refer to section 8.4 for preliminary sample sizes in the ProMetis Lx® database. Actual study size will be determined after applying all selection criteria.

- Data analysis: Descriptive analyses will be reported for all baseline variables (via appropriate measures of central tendency and inferential statistics where appropriate). Unadjusted cohort differences will be assessed using appropriate inferential statistics. Propensity score adjustment (matching or stratification) will be used to adjust for potential confounding bias. Primary and secondary outcomes will be assessed using multivariate analyses. Sensitivity

analyses will be employed as appropriate to assess the robustness of the results to the potential for unmeasured confounding and other statistical assumptions.

5. Amendments and updates

Not applicable.

6. Rationale and background

The American Heart Association's 2014 update of Heart Disease and Stroke Statistics showed that there were 1.14 million acute coronary syndrome (ACS)-associated hospital discharges in the United States (US) in 2010. Of the total hospitalizations, about 70% were for myocardial infarction (MI), while approximately 30% were associated with unstable angina (UA) diagnoses.[4] The annual direct and indirect cost of CVD and stroke in the US was an estimated $315.4 billion. Among commercially insured adults 18 to 64 years of age, the 1-year medical costs for an ACS event during 2004 to 2005 was $52,673 for those who were managed with PCI.[4]

ACS patients are managed either invasively with percutaneous coronary intervention (PCI) with or without a stent, surgically with coronary artery bypass graft (CABG), or medically without revascularization. Approximately 954,000 inpatient percutaneous coronary intervention (PCI) procedures were performed in 2010.[4] In the most current guidelines for the initial evaluation and management, hospital care, and posthospital discharge care for patients with ACS, the use of a $P2Y_{12}$ receptor inhibitor is recommended for ACS patients with planned PCI. In UA/NSTEMI and STEMI patients undergoing PCI, clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice a day should be given, generally in combination with low dose aspirin, for at least 12 months.

Prasugrel, a thienopyridine $P2Y_{12}$ receptor inhibitor, was approved by the US Food and Drug Administration (FDA) in July 2009 for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with ACS, no history of TIA or stroke, and are to be managed with PCI. The TRITON-TIMI 38 trial, a randomized clinical trial (RCT) of 13,608 patients with moderate-to-high-risk ACS with scheduled PCI, compared prasugrel to clopidogrel, both in combination with aspirin, and found that, as a more potent anti-platelet agent, prasugrel reduced the combined rate of death from cardiovascular causes, non-fatal myocardial infarction, or nonfatal stroke over a 15-month period (composite primary endpoint rate was 12.1% for clopidogrel vs. 9.9% for prasugrel).[5] The benefits of prasugrel were accompanied by an increased risk for non- CABG-related TIMI major bleeding (2.4% vs. 1.8%), including higher rates of life-threatening (1.4% vs. 0.9%) and fatal (0.4% vs. 0.1%) bleeding. Risk for non-CABG-related TIMI major or minor bleeding was also higher in patients treated with prasugrel compared to clopidogrel. Cardiovascular death and total mortality were numerically but not statistically lower for prasugrel compared to clopidogrel. When both ischemic events and bleeding were integrated into a pre-specified net clinical benefit composite end point, findings favored prasugrel. Three factors were identified through post hoc multivariate analyses as being independently associated with a a lower net clinical benefit in prasugrel-treated patients: advanced age (≥75 years), low body weight (<60 kg [132 pounds]), and a history of transient ischemic attack (TIA) or stroke. Patients with a history of TIA or stroke had increased risk of stroke with prasugrel as well as no overall clinical benefit; hence, prasugrel is contraindicated in patients with a history of TIA or stroke.[5-7]

More recently, ticagrelor, a cyclopentyltriazalopyramadine (CPTP) inhibitor of the $P2Y_{12}$ receptor on platelets, was approved by the FDA in July 2011 for the reduction of thrombotic cardiovascular events in patients with ACS. The PLATO trial, a RCT of 18,624 patients admitted

to the hospital with an ACS, with or without ST-segment elevation, demonstrated that patients receiving ticagrelor (in addition to aspirin) had a lower observed risk for the primary endpoint (a composite of death from vascular causes, MI, or stroke) relative to patients receiving clopidogrel and aspirin (composite primary endpoint rate was 11.7% for clopidogrel vs. 9.8% for ticagrelor).[8] Unlike TRITON-TIMI 38, patients in the PLATO trial did not have a requirement of being scheduled for PCI. Additionally, ticagrelor significantly reduced both all-cause and cardiovascular mortality compared to clopidogrel. There was no significant difference between the ticagrelor vs. clopidogrel groups in the risk for major bleeding as defined in the PLATO trial (11.6% and 11.2%, respectively) and according to the TIMI criteria (7.9% and 7.7%, respectively). Also, no significant differences were found in the risk for fatal or life-threatening bleeding between ticagrelor and clopidogrel. However, ticagrelor was associated with a higher rate of non-CABG related major bleeding as defined in the PLATO trial (4.5% vs. 3.8%) and according to the TIMI criteria. Ticagrelor was also associated with an increased risk for fatal intracranial bleeding (0.1% vs. 0.01%) and lower risk for other types of fatal bleeding (0.1% vs. 0.3%) compared with the clopidogrel group. When efficacy and safety were analyzed together in a pre-specified exploratory analysis, ticagrelor provided a favorable net clinical benefit over clopidogrel.

While bleeding is the most common side effect with ticagrelor and prasugrel, ticagrelor has also been shown to be associated with significantly higher rates of ticagrelor-induced mild to moderate dyspnea and predominately asymptomatic bradyarrythmias compared with clopidogrel in RCTs. These side effects are likely due to ticagrelor-induced elevations in adenosine concentrations, which are not seen with prasugrel. Patients with ACS presenting with side effects, including bleeding and dyspnea, may require additional medical attention and monitoring which may result in high medical resource utilization and costs.

Ticagrelor is twice-daily agent, whereas prasugrel is administered once daily. Although twice-daily dosing may result in suboptimal adherence as reported in prior studies, treatment patterns associated with prasugrel versus ticagrelor use in the real world have not been compared. Similar to myalgia related poor-adherence associated with statin use, real-world adherence and persistence of prasugrel or ticagrelor may be challenging as a result of side effects including bleeding and dyspnea.[7, 9]

While the results from each RCT have shown superior anti-thrombotic efficacy of prasugrel or ticagrelor in combination with aspirin over clopidogrel plus aspirin, with increased risk for non-CABG related major bleeding and on balance, an improved net clinical benefit, there is a lack of head-to-head RCTs or observational data that directly compares post-hospital discharge clinical and economic outcomes between prasugrel and ticagrelor. Direct comparison of TRITON TIMI 38 and PLATO cannot be made due to significant differences between study populations and clinical trial designs, but there have been conflicting views in terms of the differences between ticagrelor and prasugrel when the clinical efficacy and safety of these agents were indirectly compared. As such, an observational retrospective database analysis comparing net adverse clinical events (NACE) between these two agents will provide information to help address this gap. The term NACE has been used in prior studies[10, 11] to characterize the net clinical benefit for CV drugs which typically reduce major adverse cardiovascular events (MACE) at the expense of increased bleeding.

7. Research objectives

The overall hypothesis of this study is that, after adjustment for baseline differences and within a clinically relevant margin (20%), the hazard ratio and its upper 95% confidence interval of prasugrel compared to ticagrelor will not be associated with worse outcomesas measured by net adverse clinical events (NACE) up to 1 year after hospital discharge for ACS-PCI patients with no history of prior TIA or stroke .

This study will be a retrospective claims database analysis of medical and pharmacy data to examine clinical and economic outcomes of patients after index hospitalization discharge with ACS and no history of TIA or stroke, managed with PCI, and treated with prasugrel vs. ticagrelor. The specific study objectives are as follows:

7.1. Primary Objectives

- To compare NACE with prasugrel vs. ticagrelor up to one year post index hospitalization discharge.

7.2. Secondary Objectives

1. To compare demographics and baseline characteristics between patients treated with prasugrel vs ticagrelor.

2. To compare medical encounter rates of bleeding with prasugrel vs. ticagrelor at 1) 30-days, 2) six months, and 3) one-year post index hospitalization discharge [*Note*: Medical encounter rates will be stratified by i) inpatient, ii) ambulatory/outpatient, iii) emergency department (ED), stratified by whether or not it resulted in an inpatient admission, and iv) total (inpatient, ED, or outpatient)]
    - Any bleeding: ICD-9 bleeding codes or transfusion
        - ICD-9 Codes
        - Transfusion of whole blood (WB) or PRBC
            - ≥4 units
            - <4 units
    - Major / severe bleeding
        - Bleeding ICD-9 codes and ≥3 WB or PRBC transfusions during a hospitalization
        - No bleeding diagnosis code and ≥4 WB or PRBC transfusions (in-hospital) within 2 days
        - Intracranial hemorrhage
        - WB or PRBC transfusions followed by death for any reason within 72 hours

3. To compare all-cause mortality (mortality rate and time to mortality) with prasugrel vs. ticagrelor at 1) 30 days, 2) six months, and 3) one year post index hospitalization discharge

4. To compare rates of the following composite endpoints with prasugrel vs. ticagrelor at 1) 30 days, 2) six months, and 3) one year post index hospitalization discharge
    - NACE
    - MACE
    - Composite of coronary revascularization post-discharge, rehospitalization for MI, stroke, UA, TIA, or CHF
    - Composite of all-cause mortality, or rehospitalization for stroke or MI

5. To compare medical encounter rates with prasugrel vs. ticagrelor, for the following diagnoses at 1) 30 days, 2) six months, 3) one year post index hospitalization discharge [*Note*: Medical encounter rates will be stratified by i) inpatient/rehospitalization, ii) outpatient, iii) ED, and iv) total (inpatient, ED, or outpatient)]
        - MI
        - Revascularization
            - PCI
            - CABG
        - UA
        - CHF
        - Bradyarrhythmia
        - TIA
        - Stroke
        - Stable angina
        - Dyspnea
        - All-cause

6. To compare the following economic outcomes with prasugrel vs. ticagrelor at 1) 30 days, 2) six months, 3) one year post index hospitalization discharge:
    - Total inpatient hospitalization days per patient (CV-related and all-cause)
        - Percentage of patients with ≥1 inpatient hospitalization
    - Total number of medical encounters per patient (CV-related and all-cause)
        - Inpatient admissions
        - ED visits
            - Resulting in an inpatient admission
            - Not resulting in an inpatient admission
        - Outpatient visits
            - Physician and urgent care visits
            - Outpatient hospital visits
    - Healthcare charges (charged amount)
        - Total (medical and pharmacy) charges (CV-related and all-cause)
            - Total pharmacy charges
            - Total medical charges

        - Inpatient charges
        - ED charges
            - Visits leading to an inpatient admission
            - Visits not leading to an inpatient admission
        - Outpatient charges
            - Physician visits
            - Outpatient hospital
            - Other components of outpatient charges (TBD)
    - Total medical charges associated with the following diagnoses
        - MI
        - Revascularization
            - PCI
            - CABG
        - UA
        - CHF
        - Bradyarrhythmia
        - TIA
        - Stroke
        - Bleeding
        - Dyspnea

7. To describe and/or compare treatment patterns at the following time points post-index hospitalization discharge:
    - Time to first medication fill/dispensing during 30 day window
    - Switching, after initial fill during 90, 180, and 365 day windows
    - Dosing during 30, 180, and 365 day windows
    - Discontinuation during 90, 180, and 365 day windows
    - Adherence during 90, 180 and 365 day window
    - Persistence during 90, 180, and 365 day windows
    - Overall treatment duration during 30, 180, and 365 day windows
    - CV and non-CV concomitant medication use at 30, 180, and 365 days
    - Prescription pill burden at 30, 180, and 365 days
    - Co-pay amount for post-discharge index therapy at 30, 180, and 365 days

8. To assess factors associated with adherence, persistence, switching, and discontinuation of a) prasugrel, and b) ticagrelor through one year post index hospitalization discharge if statistically significant differences in treatment patterns assessed in Objective 7 are observed.

9. To examine association between treatment patterns (adherence, persistence, switching, and discontinuation) and the following outcomes for a) prasugrel, and b) ticagrelor through 1 year post index hospitalization discharge if statistically significant differences in treatment patterns assessed in Objective 7 are observed.
    - All-cause mortality

- MACE
- Any inpatient admission (CV-related and all-cause)
- Total charges (CV-related and all-cause)

7.3. Exploratory Objective

- To compare stent thrombosis-related health care resource utilization during 1) 30 days, 2) six months, and 3) one year post-discharge the index hospitalization.

8. Research methods

8.1. Study design

8.1.1. Study Overview

This will be a retrospective claims database analysis of medical and pharmacy data. This study will include data between 31 July 2008 and 01 Aug 2013. Study patients with no history of TIA or stroke will have evidence of a fill for prasugrel or ticagrelor within 30 days post-discharge from an index ACS-PCI hospitalization and any physician visit within 90 days after hospital discharge. As the purpose of this study is to evaluate how prasugrel and ticagrelor are used in a population of patients who are eligible to be treated with prasugrel, the primary population was selected as guided by the US prescribing information for prasugrel in which the indicated population is ACS patients managed with PCI. Prasugrel is contraindicated in patients with a history of TIA or stroke.[6] The ticagrelor US prescribing information has a broader label for ACS patients in that PCI is not required and there are no criteria for excluding any subpopulation of patients with ACS. It is important to note that other patients contraindicated for both prasugrel and ticagrelor, such as those with active pathological bleeding or hypersensitivity to prasugrel/ticagrelor or one of their components, cannot be identified in this database.

8.1.2. Selection Criteria

Patients in the ProMetis Lx® Database who meet all of the following inclusion criteria and none of the exclusion criteria below will be included in this study:

8.1.2.1. ACS-PCI with no prior TIA or stroke (primary study population for primary and secondary objectives)

8.1.2.1.1. Inclusion criteria

- **ACS-PCI Hospitalization**: At least one inpatient hospitalization with primary or secondary ACS diagnosis codes *and* PCI or coronary stent procedure codes at hospital discharge between 01 August 2011[1] and 31 May 2013 (selection window).
  Note:
  - The ***index admission date*** will be defined as the admission date of the first such ACS-PCI hospitalization.
  - Both the index admission and discharge dates must occur during the selection window.
- **ADP-ri Index Fill**: At least one outpatient pharmacy fill for prasugrel or ticagrelor between the index hospitalization discharge date (including the date of discharge) and 30 days post index hospitalization discharge.
  Note:

[1] The 01 August 2011 selection start date was based on the July 2011 FDA approval date for ticagrelor.

  - The *index therapy fill date* will be defined as the date of the first such fill.
  - The ADP-ri filled on the index therapy fill date will be defined as the *index therapy*.
- **Physician visit post-discharge:** At least one visit to any physician ≤90 days from the date of the ACS-PCI hospitalization discharge will be required to indicate that the patient is active in the database, as patients usually see a physician for a follow-up appointment ≤90 days of discharge for ACS-PCI hospitalization.
- **Age**: Aged ≥18 years as of the index discharge date.
- **Continuous data stability**: Continuous medical data stability during the 12 months prior to the index hospitalization discharge date (baseline period) and for at least 90 days post-discharge from the index hospitalization or until death, if sooner. The 12 month baseline period will be shortened to six months if necessary to increase sample size.

8.1.2.1.2. Exclusion Criteria

- Patients with prior TIA or stroke
- Patients with pharmacy fills for more than one ADP-ri (prasugrel, ticagrelor, clopidogrel, and ticlopidine) within 30 days following the index discharge date.
- Patients with first fill after the index event for prasugrel or ticagrelor preceding the date of discharge or >30 days after discharge from index hospitalization of ACS-PCI
- Patients with a pharmacy claim for the index medication during the prior 6 months before study index date
- Patients who first visit any physician >90 days after the ACS-PCI hospitalization discharge date

8.1.2.2. ACS-PCI population (secondary study population for additional exploration of primary and secondary objectives)

8.1.2.2.1. Inclusion criteria

- **ACS-PCI Hospitalization**: At least one inpatient hospitalization with primary or secondary ACS diagnosis codes *and* PCI or coronary stent procedure codes between 01 August 2011[2] and 31 May 2013 (selection window).
  Note:
  - The ***index admission date*** will be defined as the admission date of the first such ACS-PCI hospitalization.
  - Both the index admission and discharge dates must occur during the selection window.
- **ADP-ri Index Fill**: At least one outpatient pharmacy fill for prasugrel or ticagrelor between the index hospitalization discharge date (including the date of discharge) and 30 days post index hospitalization discharge.
  Note:

[2] The 01 August 2011 selection start date was based on the July 2011 FDA approval date for ticagrelor.

  - The *index therapy fill date* will be defined as the date of the first such fill.
  - The ADP-ri filled on the index therapy fill date will be defined as the *index therapy*.
- **Physician visit post-discharge:** At least one visit to any physician ≤90 days from the date of the ACS-PCI hospitalization discharge will be required to indicate that the patient is active in our data, as all patients should see a physician for a follow-up appointment ≤90 days of discharge from ACS-PCI hospitalization.
- **Age**: Aged ≥18 years as of the index discharge date.
- **Continuous data stability**: Continuous medical data stability during the 12 months prior to the index hospitalization discharge date (baseline period) and for up to 90 days post-discharge the index hospitalization or until death, if sooner. The 12 month baseline period will be restricted to six months if necessary to increase sample size.

8.1.2.2.2. Exclusion Criteria

- Patients with pharmacy fills for more than one ADP-ri (prasugrel, ticagrelor, clopidogrel, and ticlopidine) within 30 days following the index discharge date.
- Patients with first fill for prasugrel or ticagrelor preceding the date of discharge or >30 days after discharge from index hospitalization of ACS-PCI
- Patients with a pharmacy claim for the index medication during the prior 6 months before study index
- Patients who first visit any physician >90 days after the ACS-PCI hospitalization discharge date

8.1.3. Cohort Assignment

Patients meeting the above inclusion and exclusion criteria will be placed into two mutually exclusive cohorts based on the index therapy (prasugrel or ticagrelor).

8.1.4. Study Timeframes

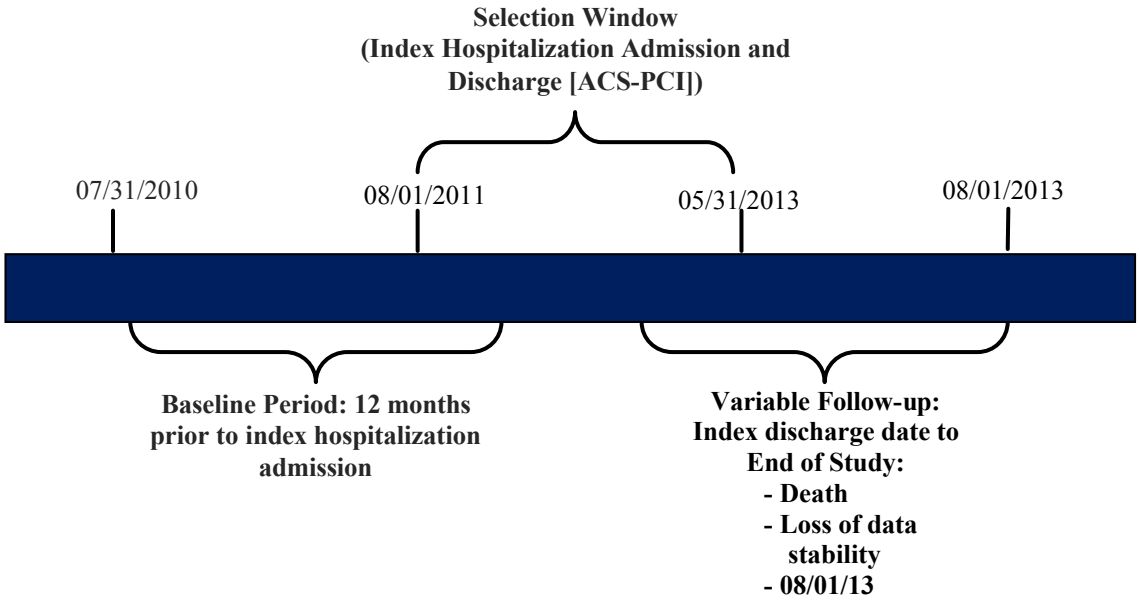
Four mutually exclusive observation periods will be defined:

- **Index hospitalization**: Days between, and including, the admission and discharge dates of the index hospitalization.
- **Baseline**: 12 months before index hospitalization admission for all primary analyses. Further patient history may be examined over the three years prior to the index hospitalization (going as far back as 31 July 2008), as a sensitivity analysis to assess patient characteristics such as history of TIA or stroke, if available.
- **ADP-ri index fill period**: Between index hospitalization discharge date (including the index hospitalization discharge date) and ≤30 days post-discharge.
- **Variable follow-up period**: Days on and after the study index date until the earliest of death, loss of data stability or end of the study period (01 August 2013). With variable lengths of follow-up, assessment of study outcomes will be adjusted by the amount of person-time observed. The follow-up period may be further stratified into intervals from the index date to 30 days, 180 days (six months), and 365 days (one year) post-discharge the index hospitalization. The variable follow up period will be used to address the primary and secondary objectives as described in section 7.2.

- **Fixed follow-up period**: Days on and after the study index date until 12 months (365 days) after the study index date or until death, if sooner. To ensure continuous stability of medical data for at least one year during follow up, a subgroup of patients with a medical claim during the first 90 days and last 90 days of follow-up will be created. The one year fixed follow-up period will be used to assess some secondary objectives including NACE at 12 months, adherence, persistence, and costs. The list of secondary objectives will be specified in the SAP.

Figure 1 below illustrates the study period and sample selection, and for simplicity, the figure does not include the index therapy selection window.

Figure 1



8.1.5. ACS-PCI with No Prior TIA or Stroke Subgroups

Sample size permitting, baseline characteristics, clinical outcomes, and healthcare economic outcomes will be examined for the following subgroups:

- <75 years of age or if ≥75 years of age, with prior MI or diabetes

Baseline characteristics and unadjusted clinical outcomes (*NACE; MACE; composite of all-cause mortality, orrehospitalization for stroke MI; or bleeding*) may be examined for the following subgroups at 6 months and one year post index hospitalization discharge:

1. Diabetes (Yes, No)
2. Geographic region at index hospitalization (Northeast, Midwest, South, West)
3. Index admission diagnosis (STEMI, NSTEMI, UA)
4. Chronic kidney disease (Yes, No)
5. Age categories at index hospitalization (<65, 65-74, ≥75)
6. Gender (Male, Female)

8.2. Variables

Baseline characteristics, procedures, and clinical outcomes

Baseline Demographic and Clinical Characteristics

- Age in years (mean and standard deviation [SD], median)
- Age (n, %)
  - 18-44 years
  - 45-54 years
  - 55-64 years
  - 65-74 years
  - ≥75 years
- Geographic region (n, %)
  - Northeast
  - Midwest
  - South
  - West
- Physician/prescriber specialty of index agent (n, %)
  - Primary care provider
  - Cardiology
  - Emergency Medicine
  - Other
- Gender (n, %)
  - Male

- Female
- Race (n, %)
  - Caucasian
  - African American
  - Hispanic
  - Asian
  - Other
- Pay type (n, %)
  - Cash
  - Medicaid
  - Medicare
  - Third party
- Pre-index ACS diagnosis (n, %)
  - MI
  - UA
- Comorbidities (n, %)
  - Anemia
  - Arterial embolism
  - Asthma
  - Atrial fibrillation
  - Cardiac dysrhythmia
  - Cardiomyopathy
  - Cerebrovascular disease
    - Stroke
      - Hemorrhagic stroke
      - Ischemic stroke
      - Unspecified stroke
    - TIA
    - Other
  - COPD
  - Deep venous thrombosis
  - Diabetes
  - Dyslipidemia
  - Dyspnea
  - CHF
  - Hemorrhagic tendencies of blood dyscrasia
  - History of bleeding
  - Hypertension
  - Hypotension
  - Ischemic Heart Disease, other than ACS (MI or UA) Liver disease
  - Obesity
  - Osteoarthritis
  - Peptic ulcer disease (PUD)
  - Peripheral vascular disease

    - Phlebitis
    - Pulmonary embolism
    - Renal impairement
        - Renal failure
        - Chronic Kidney Disease (CKD)
        - Other renal insufficiency
    - Rheumatoid Arthritis
    - Sepsis Thrombocytopenia
    - Thyrotoxicosis
- Quan-Charlson Comorbidity Index (mean and SD, median)
- Quan-Charlson Comorbidity Index (n, %)
    - 0-1
    - 2
    - 3
    - 4+

Baseline Procedural Characteristics

- Procedures prior to index hospitalization (n, %)
    - Prior CABG
    - Prior PCI
    - Prior stent implantation
        - DES
        - BMS
        - Unknown type

Baseline Treatment Utilization

- Clopidogrel (n, %)
- Phosphodiesterase inhibitors (n, %)
- P2Y12 receptor inhibitors (if prasugrel or ticagrelor, cannot be within 6 months of date of index event)
- Other platelet inhibitors (dipyridamole, cilastozol) (n, %)
- Anticoagulants (n, %)
- NSAIDs (n, %)
- HMG CoA reductase inhibitors (statins) (n, %)
- Proton Pump Inhibitors (PPIs) (n, %)
- Diabetes medications (n, %)
- Antihypertensive agents (n, %)
- Overall treatment duration for ADP receptor inhibitors (mean, SD; median days)
- Total number of medications (all) at index therapy fill date (mean, SD; median days)
- Index therapy fill date (year)
- Daily pill burden (mean, SD; median days)

- Copayment amount (standardized to 30 days supply) for index agent dispensing (mean, SD; median)

Baseline Resource Utilization and Charges

- Annual baseline resource utilization (mean, SD; median; CV-related and All-cause)
  - Inpatient (mean, SD; median; CV-related and all-cause)
    - Total number of inpatient admissions
    - Total inpatient hospitalization days
  - Outpatient (mean, SD; median; CV-related and all-cause)
    - Total number of physician visits
    - Total number of outpatient hospital visits
    - Total number of ED care visits
  - Total number of medical (inpatient and outpatient) encounters (mean, SD; median; CV-related and all-cause)
- Annual baseline charges (mean, SD; median; CV-related and All-cause)
  - Total charges
    - Pharmacy charges
    - Medical charges
      - Inpatient charges
      - Outpatient charges
        - Physician encounters
        - ED
        - Other components

Clinical Characteristics and Measures from Index Hospitalization

- Index hospitalization characteristics
  - PCI procedure (n,%)
    - DES implantation
    - BMS implantation
    - Unknown stent type
    - No stent implantation
    - Number of vessels involved
      - 1
      - 2
      - 3
      - 4+
    - Number of stents inserted
      - 1
      - 2
      - 3
      - 4+
  - CABG (n, %)

- ACS diagnosis (n, %)
  - STEMI
  - NSTEMI
  - UA
- PCI procedure per patient (mean and SD, median)
  - Number of vessels
  - Number of stents

- Index hospitalization measures
  - LOS (mean and SD, median)
  - Any bleeding (n, %)
    - Major/severe bleeding (n, %)

Post Index Discharge Outcomes

Post Index Discharge Clinical Outcomes

- Any bleeding (n, %)
  - By ICD-9 codes or transfusion
    - By ICD-9 Codes
    - By Transfusion of WB or PRBC
      - ≥4 units
      - <4 units
- Major / severe bleeding (n, %)
  - Bleeding ICD-9 codes and ≥3 WB or PRBC transfusions (in-hospital)
  - No bleeding diagnosis code and ≥4 WB or PRBC transfusions within 2 days (in-hospital)
  - Intracranial hemorrhage
  - WB or PRBC transfusions followed by death for any reason within 72 hours
- All-cause mortality (n, %; time to event [mean, SD, median])
- Composite outcomes (n, %; time to event [mean, SD, median])
  - NACE
  - MACE
  - Composite of coronary revascularization post-discharge, rehospitalization for MI, stroke, UA, TIA, or CHF
  - Composite of all-cause mortality, or rehospitalization for stroke or MI
- Medical encounters for the following events [n, %; stratified by i) inpatient/rehospitalization, ii) outpatient, iii) ED, and iv) total (inpatient, ED, or outpatient)]
  - MI
  - Revascularization (excluding the index PCI procedure)
    - PCI
    - CABG
  - CHF

- Bradyarrhythmia
- TIA
- Stroke
- UA
- Stable angina
- Stent thrombosis
- All-cause (any reason)
- Dyspnea

Post Index Discharge Economic Outcomes

- Total inpatient hospitalization days (mean, SD; median; CV-related and all-cause)
- Total number of medical encounters (mean, SD; median; CV-related and all-cause)
    - Inpatient admissions
    - ED visits
        - Visits resulting in an inpatient admission
        - Visits not resulting in an inpatient admission
    - Outpatient visits
        - Physician visits
            - Primary care provider
            - Cardiology
            - Other
        - ED visits not resulting in an inpatient admisson
        - Outpatient hospital visits
- Total (medical and pharmacy) charges (mean, SD; median; CV-related and all-cause)
    - Total pharmacy charges
        - ADP receptor inhibitors
    - Total medical charges
        - Inpatient charges
            - Components of inpatient charges (components of interest TBD)
        - ED charges
            - Visits leading to an inpatient admission
            - Visits not leading to an inpatient admission
        - Outpatient charges
            - Physician visits
                - Primary care provider
                - Cardiology
                - Other
            - Outpatient hospital
            - Other components of outpatient charges, including urgent care facilities
- Total medical charges associated with the following diagnoses (mean, SD; median)
    - MI
    - Revascularization

        - CABG
        - PCI
    - CHF
    - UA
    - Bradyarrhythmia
    - TIA
    - Stroke
    - Bleeding
    - Dyspnea

Post Index Discharge Treatment Patterns

- Time to first medication fill/dispensing (in days, mean, SD; median)
- Switching from index therapy to the following ADP-ri (n, %, time to)
    - Clopidogrel
    - Prasugrel
    - Ticagrelor
- Dosing for ADP-ris
    - Index therapy
        - Daily dose (mean, SD, median)
    - Clopidogrel
        - Daily dose (mean, SD, median)
    - 5mg prasugrel dose (n, %)
- Discontinuation (n, %)
- Adherence (mean, SD; median)
- Adherence (n, %)
    - <20
    - 20-<40%
    - 40-<60%
    - 80-100%
    - <80%
- Persistence (mean, SD; median days)
- Overall treatment duration (mean, SD; median days)
- Concomitant medication use (n, %)
    - Digoxin
    - Statins
    - Anticoagulants
    - NSAIDs
    - Calcium channel blockers
    - ACEi/ARB
    - Beta blockers
    - Proton pump inhibitors
    - CYP3A4 inducers and inhibitors
        - CYP3A inhibitors

    - CYP3A substrates with narrow therapeutic indices
    - CYP3A inducers
- Concomitant medication use (mean, SD; median)
- Daily pill burden (mean, SD; median)

8.3. Data sources

8.3.1. ProMetis Lx® database

ProMetis Lx integrates healthcare claims data from physician practices, pharmacies, and hospitals for a broad, longitudinal view of healthcare delivery and patient usage patterns. With the ability to link healthcare activity from multiple data sources using a unique patient identifier, over 70% of patients in the sample have diagnosis information available. ProMetis Lx creates a resource with the capability to support a wide range of patient-centric studies, including practitioner and patient tracking.

ProMetis Lx database is an unprojected data source that includes 73% of all retail and mail-order prescriptions filled in the United States (US) and provides enhanced local level insight into treatment patterns and patient behavior. This coverage includes up to 60% of all specialty pharmacy prescriptions. The database includes 55% of medical office and 30% of hospital inpatient claims in the US. The hospitals that are captured in the database are larger 100+ bed hospitals.

The ProMetis Lx suite is designed to examine patient treatment and medication consumption behavior and empower more informed decisions through access to current and historical patient trends for products within a market or by diagnoses. ProMetis Lx offers the ability to segment by patient and practitioner characteristics associated with therapy, including patient age and gender, prescriber specialty and geography, payment type, medical conditions and diseases (diagnoses), and surgical and non-surgical procedures (Current Procedural Terminology [CPT] codes).

As is the case with other large administrative claims databases, this longitudinal patient level database does not contain VA/military pharmacy information for patients that fill prescriptions and receive treatment within those facilities. ProMetis Lx is a patient-level, integrated database with representative geographic coverage. It is representative of the census population across age, sex, geography and includes patients from a wide representation of plans. The unique patient-level linking process provides a longitudinal view of patient history as patients move across providers and payers. ProMetis captures and integrates patient activity across prescription, physician practice and hospital administrative claims from providers that contribute data to the Prometis system. Other databases are plan-centric, and if a patient happens to change payers over time, the longitudinal history of that patient is lost and the patient may be considered a new patient in such a database inaccurately. Although claims are not restricted at the plan level in Prometis, claims from providers who do not submit data to the system are not captured.

8.3.2. Mortality data

To meet the objectives of our study, the ProMetis database will be linked with the Social Security Death Index (SSDI). The SSDI database of death records is extracted from the US Social Security Administration's Death Master File Extract. The SSDI database lists all persons

with a Social Security number who have died since 1963 and whose death was reported to the Social Security Administration. A third-party vendor then attempts to match data from the SSDI with patients included in the ProMetis data using a variety of personal identifiers. Therefore, for each patient who can be matched to the SSDI and who died before the study cutoff date of 08/01/2013, a mortality date will be provided. Date of death will be identified for all patients who died before the study end. Cause of death is not available; therefore, only all-cause mortality will be assessed. There is a data lag time of 12 weeks following the end of each calendar month. After patients are linked with the SSDI, these data can be used to inform sample selection. For example, patients that might otherwise be removed from the study due to insufficient continuous enrollment may be included if they were observed to have disenrolled because of death.

8.4. Study size

Table 1 provides preliminary sample sizes available in the ProMetis database for patients with 1) ACS managed with PCI, 2) at least 18 years of age, 3) at least one outpatient pharmacy fill for prasugrel or ticagrelor within 30 days post index hospitalization discharge, 4) no history of the index medication during the 6 months prior to the index hospitalization, 5) no history of stroke or TIA in the 12 months prior to the index hospitalization, 6) at least one medical claim after the index ACS-PCI hospitalization, and 7) at least one medical claim prior to the index ACS-PCI hospitalization.

Table 1. Preliminary Count of Patients Available for Analysis as of Cut-off Date of 01 August, 2013

Step	Subset of Step	Criteria	Count
1.		Patients with an ACS Diagnosis AND a PCI procedure on discharge claim between August 2011 and May 2013.	**173,484**
2.		Patients aged ≥18 years	**173,461**
3.		Patients with a claim for prasugrel or ticagrelor within 30 days of ACS-PCI	**36,378**
4.		Patients with a claim for only one of two index medications within 30 days of ACS-PCI	**36,100**
5.		Patients without a claim for index medication in 6 months prior to ACS-PCI	**34,838**
6.		Patients without a claim with diagnosis for stroke or TIA in 12 months prior to ACS-PCI	**33,566**
7.		Patients with any inpatient or outpatient claim within 90 days of ACS-PCI	**29,393**
8.		Patients with any inpatient or outpatient claim within 6 months prior to ACS-PCI	**22,766**
	a.	Those taking prasugrel	**18,191***
	b.	Those taking ticagrelor	**4,575***

***** These counts are preliminary and were provided by data vendor. A period of 12 months prior to the index date may be used to identify patients with any prior medical claims to ensure data stability rather than 6 months; therefore, patient counts may be higher than presented.

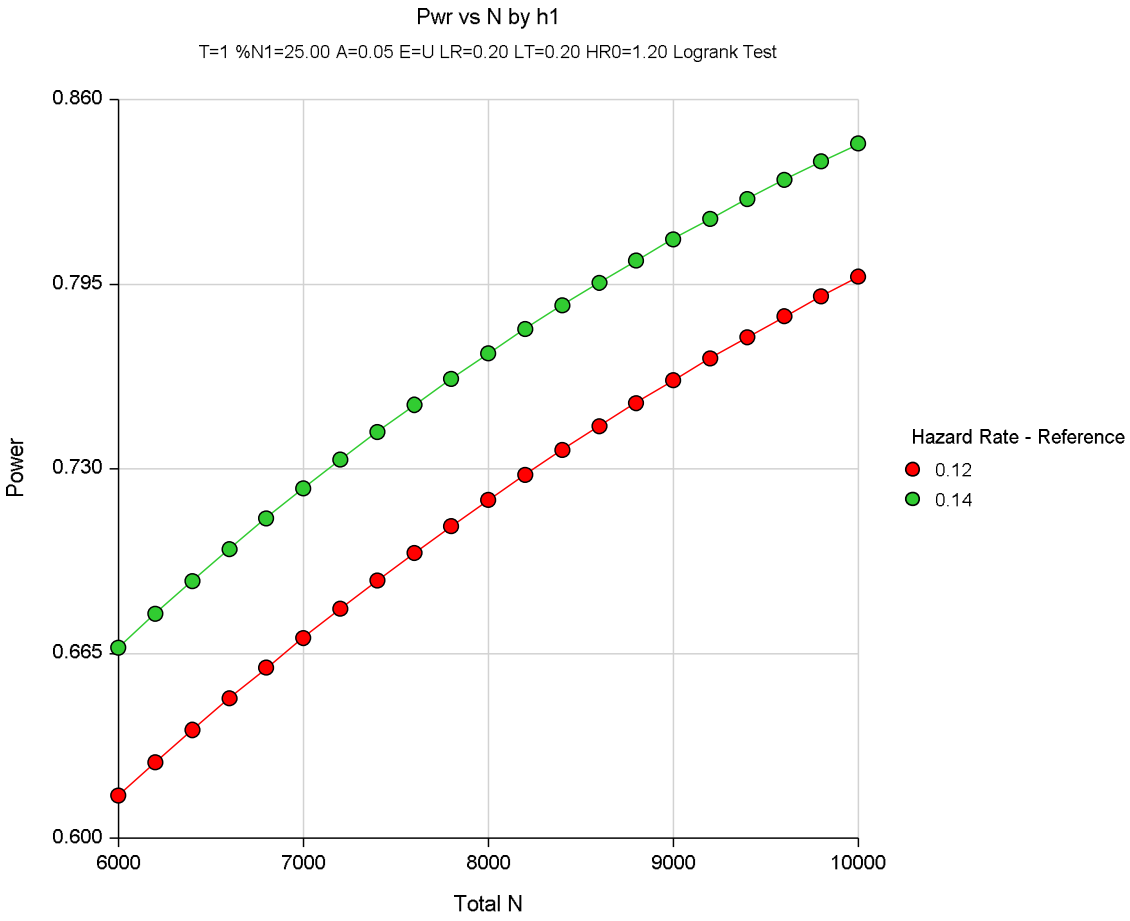
8.4.1. Sample Size

Power analyses were conducted to assess the sample sizes required to provide over 80% statistical power to declare that after adjustment for baseline differences, the hazard ratio with upper 95% confidence interval of prasugrel compared with ticagrelor will not be associated with worse outcomes within a clinically relevant margin (20%), in regards to net adverse clinical events (NACE) up to 1 year. Given recent observational data (study alias H7T-US-B019)[11] showing an adjusted 90 day post-discharge NACE rate of approximately 10%, a power analysis assuming a) base rates of 12% and 14% for NACE up to one year excluding the index hospitalization, b) a margin in which the upper limit of the 95% CI for the point estimate should not exceed 1.2, c) a drop-out rate of 20% in both treatment arms, and d) a one-sided alpha level of 0.05 (one-sided 95% confidence interval), is presented below. The 1.2 margin specified for the current study is an acceptable clinically relevant difference as also used in prior CV studies.[11-14]

As shown in Figure 2, a logrank test indicates that an overall sample size of 10,000 subjects (2,500 in the ticagrelor group and 7,500 in the prasugrel group, if a 1:3 matching ratio is used) with a reference group NACE event rate of 12% will achieve approximately 80% power at a 0.05 significance level to detect an equivalence hazard ratio of 1.20 when the actual hazard ratio is an equivalence hazard ratio of 1.00. An overall sample size of 8,800 subjects (2,200 in the ticagrelor group and 6,600 in the prasugrel group, if a 1:3 matching ratio is used) with a reference group NACE event rate of 14% will achieve approximately 80.3% power at a 0.050 significance level to detect an equivalence hazard ratio of 1.20 when the actual hazard ratio is an equivalence hazard ratio of 1.00.

If the sample size obtained after the application of all inclusion and exclusion criteria is less than specified above, a higher matching ratio (such as 1:5) may be used, or patients may be stratified instead of matched by propensity score.

Figure 2



8.5. Data management

Datasets and analytic programs will exclusively maintained, accessed, and analyzed by researchers at Evidera. No patient level data will be transferred to the study sponsors. Evidera will store all the study-related datasets, including the final analytic datasets, according to regulatory requirements. However, the tables and figures generated from the aggregate data will be shared with the sponsors.

8.6. Data analysis

Statistical analyses will be performed to address each of the study objectives. All analyses will be conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC). A *P*-value of 0.05 will be considered statistically significant with no adjustment for multiple comparisons. The Benjamini-Hochberg method[15] may be used as appropriate, particularly for analyses related to secondary

objectives, to control for the multiplicity effect and mitigate the likelihood of obtaining any type 1 error.

8.6.1. Missing Data

No imputation of missing data will be conducted for outcome variables, and it will be assumed that missing outcomes did not occur. If the amount of missing data is substantial (>20%) for a particular patient characteristic, then this characteristic may be excluded from any predictive models or other sensitivity analyses may be considered as appropriate. Details will be provided in the statistical analysis plan.

8.6.2. Potential Outliers

Outliers, such as patients with extremely high values (e.g., charges), are typical in observational research and can have a very strong impact on the estimated mean values in any cohort. In this analysis, values beyond the interquartile range (IQR) by more than 1.5 times the range may be flagged as potential outliers. Potential outlier values will be examined prior to conducting the primary analysis of charge data.[16] As the goal is to estimate the raw means in each cohort, outlier values in general will be included in the analysis. However, outlier values that are considered to be implausible may be truncated (Windsorized) to a maximum plausible value. Determination of any implausible charge values will be made prior to conducting the outcome analysis and will be made blinded to the cohort membership of individual patients. Sensitivity analyses may be conducted to test the implications of any alterations to the original data.

8.6.3. Descriptive Analyses

Demographic, clinical, and other baseline variables (including resource use and cost) will be summarized by cohort and for overall group as the counts and percentages for categorical variables and means, median, standard deviation, min, max, and IQR for continuous variables. Differences between cohort will be assessed using Chi-square tests for categorical variables and t-tests and ANOVA for continuous variables. Exact tests and/or nonparametric tests will be used as appropriate.

Dosing

The mean daily dose of the index therapy, and the percentage of patients filling a 5 mg dose of prasugrel during follow-up will be assessed. For patients who switch to clopidogrel, the mean daily dose for clopidogrel will also be assessed.

Daily pill burden

Daily pill burden will be estimated by dividing the quantity of filled medications supplied during a specified time period (e.g., 12-month baseline period or 6- or 12-month follow-up) by the total days in that time period (e.g., 180 or 365).

Quan-Charlson Comorbidity Index

The Quan-Charlson Comorbidity Index contains 17 comorbid conditions identified using primary and secondary ICD-9 diagnosis codes during the baseline period (see Annex 1).[17, 18] Each of the 17 conditions is assigned a weight or score of 1, 2, 3, or 6 depending on the risk of

death associated with the condition. The overall comorbidity score is the sum of associated weights for any of the 17 conditions present during the baseline period (maximum possible score of 29). The Quan-Charlson Comorbidity Index will be grouped into the following categories: 0-1, 2, 3, and 4+.

8.6.4. Unadjusted Analyses

Unadjusted outcomes and treatment patterns will be compared using the same methods described in the descriptive analyses section above. In addition, Kaplan-Meier curves along with log rank tests will be used to evaluate persistence (time to discontinuation), switching (time to), and survival (time to death), time to first occurance of a net adverse clinical event, and time to first occurance of a major adverse cardiovascular event.

8.6.5. Bias Adjustment: Propensity Score Approach

Propensity score adjustment has been reported to eliminate 85% to 90% of the treatment bias in observational cohorts.[19, 20]

Matching Approach
Propensity score matching will be initially employed to adjust for potential confounding bias.[19, 20] The first step would be to estimate propensity scores for each patient using a forward step-wise logistic regression model with prasugrel cohort membership as the binary outcome measure and *baseline demographic and clinical characteristics*, *index hospitalization procedural characteristics and measures (LOS and bleeding), baseline treatment utilization*, and *baseline resource utilization and charges* as the independent variables in the model. These independent variables were selected *a priori* based on literature and expert opinion as potentially moderately related to both cohort and outcome or strongly related to either cohort or outcome.[21-27] A 0.10 significance level will be used for independent variables entering and remaining in the model.

The step-wise regression model building process will begin by evaluating each of the candidate independent variables and selecting the variable with the largest score chi-square statistic. If the p-value for this variable is less than the pre-specified model building significance level (0.10), then this variable will be entered into the propensity model (logistic regression model) as the 1st independent variable. At step 2, the score chi-square statistic for each remaining candidate variable will be evaluated and the variable with the largest test statistic will then also be added to the propensity model as long as its p-value is less than 0.10. Before moving to step 3, the chi-square p-value for each variable in the propensity model will be re-examined (because values from existing variables in the model may change once the new variable is introduced) and the variable will be removed from the model if the p-value was no longer <0.10. This process will be continued until all candidate independent variables are entered in the model or until none of the remaining candidate independent variables met the 0.10 significance level requirement for entering the model.

A greedy 1:1 matching algorithm will first be utilized to match each ticagrelor patient with an appropriate prasugrel patient based on propensity scores. However, a higher matching ratio (up to 1:5) may be used to increase sample size if necessary.

> *Note:* Three separate propensity matches will be done – primary population, secondary population, and subgroup #1.

Stratification Approach

If propensity score matching cannot produce balanced matched cohorts with at least 90% of the ticagrelor sample, then propensity score stratification will be used. For propensity score stratification, the estimated propensity scores for each patient will then be grouped into 10 strata based on deciles of the propensity score distribution. The frequencies of patients from each cohort will be summarized by strata to ensure sufficient number of patients from each cohort for comparisons.

Prior to initiating the outcome analysis, the quality of the propensity score adjustment and associated assumptions will be evaluated (e.g., using significance testing, assessment of standardized differences).[28] As a rule of thumb, standardized differences greater than 0.10 indicate imbalance that may require further investigation.[29] The balance diagnostics may identify imbalances that result in the need for a revision to the propensity score model, the need for specific sensitivity analyses, or other modifications to the analysis plan. Any modifications to the propensity model will be finalized prior to initiating analysis of the outcome measure.

8.6.6. Propensity Adjusted Outcomes Analyses

The adjusted (propensity score matched or stratified) analyses will be considered the primary analysis for the primary objective and secondary objectives 2-6. To examine whether the hazard ratio and associated 95% CI of prasugrel compared to ticagrelor is not worse by more than 20%, a one sided test (alpha 0.05) will be conducted to compare categorical outcomes between prasugrel and ticagrelor and the upper limit of the 95% confidence interval of the hazard ratio (prasugrel vs ticagrelor) from the Cox proportional hazards model will be compared with 1.2. In addition, two-sided tests (alpha 0.05) will be used to assess primary and secondary outcome differences between the two drugs, as appropriate.

8.6.6.1. Analysis of Primary Objective

In addition to KM curves, multivariate Cox proportional hazards models will be used to assess the primary objective using a *on treatment* approach where patients will be censored at the end of index treatment exposure time window (time of discontinuation or switching to any ADP-ri). In addition, the following analytic approaches may be conducted as secondary objectives:

- an *extended on treatment* approach, where patients will be censored when they discontinued or switched to any ADP-ri other than clopidogrel.

- an *as treated* analysis approach, where patients treatment will be reassigned as the one they switched to. If multiple switches occurred, the one nearest to the first MACE event will be selected.
- a fixed time period approach where all patients with 12 months follow up will be analyzed and their treatment cohorts are based on the index therapy regardless if they switched to any ADP-ri or not.

A 95% Confidence interval (only the upper bound) for the hazard ratio will be constructed. The upper bound will be compared to 1.2 to test whether prasugrel is not associated with much worse outcomes compared to ticagrelor in regards to net adverse clinical events (NACE) up to 1 year.

8.6.6.2. Analysis of Secondary Objectives

Adherence
PDC will be calculated by dividing the total days supply of filled medications during the 12-month interval by 365 days. For purposes of this study, the days supply of overlapping fills will be pushed out to start the day after the end of the previous fill's supply. The calculation will be corrected for inpatient admissions, under the assumption that during a hospitalization medication was supplied by the facility. PDC ≥ 80% will be considered adherent, and adherence will be capped at 100%. Adherence will first be calculated without restrictions based on data stability. If adherence estimates are ≥20% lower than previously published studies report for prasugrel,[30] patients assessed for adherence will be restricted to those with a pharmacy claim for any medication in the first three and last three months of the one year follow-up period to ensure that a patient has available pharmacy claims for the full 12 month follow-up period.

Discontinuation
The date of discontinuation will be defined by the run-out of days supply of the last prescription filled prior to the first 30-day gap in treatment, if any. The days supply of overlapping fills will be pushed out to start the day after the end of the previous fill's supply.

Discontinued therapy if:
- (End of study period) – (run-out date of last fill) ≥ 30 days

OR
- (start date of fillx+1) – (run-out date of fillx – 1) ≥ 30 days

Persistence
Persistence with the post-discharge index therapy will be calculated as the number of days from the index date to the date of discontinuation. The follow up period may be shortened to (time period – 30 days) to allow for the determination of a gap, if any, within the follow up period.

Healthcare Charges and Costs
Healthcare charges will be calculated for inpatient admissions, emergency department visits, ambulatory care visits (including outpatient hospital care, physician services, and other ancillary services like physical therapy, laboratory and radiology services), and outpatient pharmacy fills. Total charges will be calculated as the sum of all medical and pharmacy charges. Charges will be calculated for all patients in the study cohort. All charges will be adjusted for inflation to 2013

US dollars using the coordination of benefits (COB) and the annual medical care component of the Consumer Price Index (CPI) to reflect inflation between study start and end dates.

The Prometis database contain data on total charges which represent the amount that providers bill for services, but does not reflect how much services actually cost or the specific amounts that providers received in payment. To estimate how these charges translate into actual costs, appropriate and citable cost-to-charge ratios may be used to convert charge data to cost estimates by multiplying total charges with the cost-to-charge ratio.

8.6.6.2.1. Categorical Outcomes

If propensity score matching is used:
McNemar's test may be used to assess the statistical significance of a difference in proportions for categorical outcomes.

If propensity score stratification is used:
Categorical (binary) outcome variables associated with both the primary and secondary objectives, including separate endpoints for bleeding, mortality, and dyspnea rates, may be assessed as dependent variables using Cochran-Mantel-Haenszel (CMH) test or ProcGenMod model controlling the propensity score strata. The interaction between treatment and strata may be further examined and if the interaction term turns out to be significant, the relative risk in each strata will be outputted to examine the variability across the strata. The upper limit of the 95% confidence interval of the relative risk (prasugrel vs ticagrelor) from Cochran-Mantel-Haenszel test stratifying by propensity score strata will be compared with 1.2.

Cohort differences will be summarized using both the estimated relative risk and risk differences from the model. If logistic regression is used, the estimated risk differences from the final model will be computed by subtracting the average predicted probability of categorical outcomes with prasugrel across all patients from the predicted probability of categorical outcomes with ticagrelor across all patients. The number needed to treat (NNT) and number needed to harm (NNH) will be defined as the inverse of the risk difference (1/risk difference).

The risk factors for the discontinuation, switching , and adherence will be examined using logistic regression. All variables included in the propensity score model will be considered as potential factors.

8.6.6.2.2. Continuous Outcomes

If propensity score matching is used:
Generalized linear model (GLM) with gamma distribution and log link function will be used to compare cost and resource use outcomes between the two cohorts. Poisson and/or negative binomial distribution may be used as appropriate. The method of generalized estimating equations (GEE) may be considered for the matching correlation between two treatment.

If propensity score stratification is used:

Cohort differences in continuous outcome variables may be analyzed using GLMs to model charges (with gamma specification) as well as resource use outcomes and treatment patterns (with Poisson and/or negative binomial specifications). For example, considering the truncation of adherence values to 1, there may be a violation of the normality assumption; therefore, a GLM with negative binomial distribution will be used to model adherence as a continuous measure. The negative binomial regression has been shown to account for possibility of over dispersion than would be expected by a simple Poisson distribution. Treatment cohort (prasugrel or ticagrelor), propensity score strata, and the cohort-by-propensity score strata interaction term may be included as independent variables in the models. Least squares means and 95% confidence intervals will be estimated on the difference in mean charges. Alternative and more appropriate methods (e.g., propensity score bin bootstramping method to assess charges) may be employed after assessment of the observed distribution of continuous dependent variables and prior to any outcomes analyses.

Multivariate Cox proportional hazards models will be used to compare persistence (time to discontinuation), switching (time to), and survival (time to death), time to first occurrence of a net adverse clinical event (secondary endpoint, i.e., 6 month timeframe), and time to first occurrence of a major adverse cardiovascular event. Patients will be censored at the time of index drug discontinuation or switching.

Multicolinearity and interaction between independent variables for all afore mentioned regression models will be examined and addressed as appropriate.

8.6.7. Sensitivity Analyses

The following sensitivity analyses may be performed.

1. To assess the robustness of the results to the potential for unmeasured confounding (confounding variables not captured in the analysis database, such as patient weight, BMI, and smoking status), a sensitivity analysis will be conducted using the rule-out method.[31]

   The rule-out method graphically depicts the level of unmeasured confounding necessary to explain the observed treatment difference. The level of unmeasured confounding is quantified by 1) the association between the unmeasured confounder and treatment choice; and 2) the association between the unmeasured confounder and outcome. While the true level of unmeasured confounding remains unknown, if the rule-out method demonstrates that it would require very strong levels of unmeasured confounding to eliminate ('rule out') the observed treatment difference, then the analysis is considered more robust than if only weak levels of unmeasured confounding would rule out the observed result. The Bayesian approach will also be considered as appropriate.

2. To assess the robustness of the results to modeling assumptions, method selection, and other statistical assumptions, alternative methods may be used as appropriate. Although Central Limit Theorem (CLT)-based methods are more sensitive to extreme distributions in small samples, the current study sample is large enough to justify their efficiency and reliability in analyzing charges.[32] Therefore, CLT-based methods (ANCOVA or traditional OLS models) will be used as a sensitivity analysis of charges and other continuous dependent variables.

The list of independent variables will be consistent with the one used in the primary analysis. Multivariate logistic regression without propensity stratification may be used as sensitivity analysis for categorical outcome variables. Independent variables will include all independent variables in the final propensity model. Bootstrapping (e.g., for cost and any other skewed outcomes) may be conducted as appropriate. Generalizability of the results may be assessed by examining any exclusion of patients during the selection process.

Note: If propensity score matching is used for adjustment in the primary analysis, then sensitivity might include using propensity score stratification and the same outcomes model used in the primary analysis. If propensity score stratification is used for adjustment in the primary analysis, then sensitivity might include using the same propensity model with a different outcomes model OR run a regression model without propensity adjustment (i.e., using the actual covariates as independent variables)

3. Sensitivity analyses may also be conducted using the primary methods/models with the following exceptions:

    a) Exclude patients selected during the first 3 months of the enrollment window (i.e., use a selection window start date of 11/01/11 instead of 08/01/11) as ticagrelor was launched in 08/2011 and the use of the new therapy in the first few months after launch may differ from how the treatment is used after a few months of experience
        Note: This new population will require a new propensity model, only if sample size allows statistically
    b) Define CV-related medical encounters and cost using a primary diagnosis only instead of primary or secondary diagnoses
    c) Exclude patients with less than 31 total supply days of index therapy over the 1 year post-index period,
    d) Define discontinuation as an index medication gap ≥ 60 days;
    e) Define the study index date = the index therapy fill date; instead of index hospital discharge date as in the primary analysis
    f) Use 70% and 90% as adherence cut-offs instead of 80%
    g) Not counting patients who switch to another ADP-ri as discontinuations
    h) Include patients with multiple qualifying index therapy fills (between the index admission date and 30 days post index hospitalization discharge) and consider the first qualifying therapy as the index therapy
    i) Allow variable baseline period for all patients (i.e., extend the baseline period going as far back as 31 July 2008)
    j) If treatment pattern analyses indicate much lower adherence and persistence than can be expected from prior research,[30] a secondary analysis of adherence, persistence, and costs over the 1 year follow-up period may be performed in a subgroup of patients with a pharmacy claim for any medication during the first 90 days and last 90 days of follow-up to ensure the stability of pharmacy data during this assessment period.

The specific models and list of sensitivity analyses will be finalized in the SAP prior to conducting the analyses.

8.7. Quality control

An Evidera data analyst will write and review programs to implement analyses outlined in the SAP. The project team will review all data output, including SAS code as needed. Changes and corrections to programs stemming from the review will be made as appropriate. All programs will be saved and the process will be documented.

All work will be subject to quality control and documentation procedures to make certain the report is accurate and thorough, and the analyses can be reproduced. If the data do not permit an analysis as planned (e.g., through insufficient sample size in a stratified analysis, Evidera staff will inform Lilly/DSI and include this information in the study report.

8.8. Limitations of the research methods

While claims data are extremely valuable for assessing health care outcomes, treatment patterns, health care resource utilization, and charges, all administrative claims databases have inherent limitations because the claims are collected for the purpose of payment and not research.

- Data on patient enrollment is not available in this database. Enrollment will be inferred through the presence of at least one medical claim within 90 days of the index hospitalization discharge date. If a large proportion of patients have gaps without medical claims >6 months during follow-up, further analyses will be performed to mitigate this limitation, potentially including censoring a patient on the date of the last observed medical claim.
- Data on mortality is provided by the Social Security Death Index (SSDI) and patients with a mortality record in the SSDI may not always be matched to a patient in the ProMetis dataset. Any missing data on mortality is assumed to be random and not associated with prescription of either index medication (i.e. prasugrel or ticagrelor), although the possibility exists that this assumption may be incorrect. In addition, the SSDI utilizes a probabilistic (not deterministic) matching algorithm to link identifiers from user provided data with death certificate information.
- As the databases are based on a large convenience sample, a limitation of its interpretation is that the results may not be generalizable to other populations.
- ACS events or underlying diseases prior to the database time frames may not be captured.
- All medical conditions will be identified based on administrative claims with no access to medical charts. Therefore, data entry and coding errors are always a concern, especially as they may affect identification of patients with some outcomes of interest (e.g., dyspnea). The impact of such errors in coding on the current study is unknown. Furthermore, since unique ICD-9 codes do not exist for some of the outcomes of interest (e.g., to allow discrimination between drug induced vs other causes of dyspnea), the sensitivity and specificity of the proposed methods to identify patients with some of these outcomes is not known. Additionally, baseline characteristics such as a prior MI or revascularization procedures may not be captured if they occurred greater than 1 year prior to the index hospitalization.

- An administrative claim for a dispensed prescription does not necessarily indicate that the drug was consumed or that it was taken as prescribed; calculations of medication adherence and persistence will only approximate true treatment patterns.
- For purposes of this analysis, treatment switches to another oral OAP (e.g., clopidogrel) will be counted as discontinuations. Because the term *persistence* is typically used to describe a patient's behavior, referring to a treatment switch as nonpersistence may suggest that the patient failed to take the product as directed even though the patient followed the directions appropriately.
- Data contained in ProMetis is at the provider/facility level. Care provided by facilities who do not contribute data to ProMetis will not be included in the study dataset.
- Over the counter medications, such as aspirin, are not captured in the pharmacy database.
- Several potential confounders, including socioeconomic status, weight, body mass index, and obesity (a known risk factor for dyspnea and stroke) are not generally available for analysis in such data. Additionally, provider characteristics (e.g., gender, years in practice) and organizational (formulary) characteristics that may influence the access and choice of medications are not available from this data source.
- Capitated claims will be included in the cost analyses as they comprise a large proportion of administrative claims database. Due to reimbursement differences, the cost data associated with capitated claims may be less accurate than fee-for-service claims. Therefore, plan type will be adjusted for as a covariate in the final model.
- Prometis includes outpatient pharmacy claims only; therefore, patients will be assigned to treatment cohorts based on first fill within 30 days post discharge from the index hospitalization. As a result, the medication used between the date of discharge from the index hospitalization (study index date) and the first outpatient prescription fill is not known and index hospital drug use cannot be accounted for during propensity score adjustment. This is not expected to be a major limitation in this study because a) it is unlikely that the medication prescribed for the patient at discharge from the index hospitalization will be different from the prescription filled during the ADP-ri index fill period, b) events and other factors (e.g., procedural characteristics) during the index hospitalization (which could influence the drug prescribed at discharge) will be included as covariates in the propensity adjustment model, and c) prior CV studies have shown that most prescriptions are filled within 1 week after discharge from an ACS event.[30, 33]
- The type of PCI (planned or unplanned) during the index hospitalization and post-discharge cannot be determined using administrative claims. A medical chart review will not be performed.
- As with most administrative claims datasets, the Prometis database does not capture medical and pharmacy information from all healthcare providers in the US. However, the data are representative of the census population across age, sex, geography and include patients from a wide representation of plans. Because of the stringent requirements imposed upon data suppliers, the Prometis database contains patients who are accurately linked longitudinally across healthcare settings. This provides assurance that the same patient is followed. Given the relatively short duration of this study, it is unlikely that a large number of patients will change providers during the study period. Nevertheless, for purposes of this study, patients will be required to meet an eligibility criteria for having claims pre- and post- the index hospitalization (data stability criteria), which imposes a

'closed sample' criteria and ensures that there is no loss to the patient's visibility during the study period.

- While the *on treatment* approach (primary analysis strategy) will ensure that outcomes are properly attributed to the index therapy, patients whose outcomes are unknown at time of switching or discontinuation will be censored. Implications of this (i.e., assuming that none of those censored patients experience the target outcome after discontinuation or switching) on event rates and study power are unknown. However, alternative analysis strategies will be employed as described in section 8.6.6.1 in order to mitigate this potential limitation by including all outcome data for all eligible study patients during the follow up period, regardless of their adherence status to the index therapy.

8.9. Other aspects

N/A

9. Protection of human subjects

This study will be conducted in accordance with applicable laws and regulations of the region, country or countries where the study is being conducted, as appropriate.

Patient records from the ProMetis database have been de-identified in compliance with Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data contained in the database have been previously gathered by healthcare providers (hospitals, providers and pharmacies) in the course of their regular operations for financial and clinical benchmarking and reporting (eg, reporting to Centers for Mediare and Medicaid Services [CMS]) purposes.

Since no identifiers of patients, such as names, social security numbers, or actual birth dates are available in the database, it is not possible to return to patients in order to obtain consent; thus, no patient consent will be obtained for study purposes.

Also, because these data are de-identified and analyses of the data are retrospective, observational, and non-interventional in nature, IRB review was deemed unnecessary and would have been considered 'EXEMPT'.

Data from the ProMetis database will not be transferred to Lilly and/or DSI.

10. Management and reporting of adverse events/adverse reactions

During the course of this retrospective observational research study, information pertaining to adverse reactions (ARs) will not be discovered as the study does not involve identifiable patient data associated with a Lilly drug. The data in this study is only being analyzed in aggregate, study data sets do not include safety measures, and there will be no medical chart review or review of free text data fields.

11. Plans for disseminating and communicating study results

At least 2 abstract submissions are planned for immediate dissemination at a national congress with the appropriate audience: (1) focused on the clinical endpoints; and, (2) focused on the economic endpoints. A primary manuscript containing all of the study results is planned. Additionally, a manuscript focusing on the health care resource use and charges will be considered.

12. References

Provided as footnotes where relevant.

Annex 1. Additional Information

Table 1. Quan-Charlson Comorbidity Score: Weighted Index of Comorbidities

Assigned Weight	Condition
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Rheumatologic disease
	Peptic ulcer disease
	Mild liver disease
	Diabetes without chronic complication
2	Diabetes with chronic complication[3]
	Hemiplegia or paraplegia
	Renal disease
	Any malignancy, including leukemia and lymphoma
3	Moderate or severe liver disease[4]
6	Metastatic solid tumor[5]
	AIDS/HIV

[3] If "diabetes without chronic complication" and "diabetes with chronic complication" are both captured during baseline period, then (of the 2 conditions) only count "diabetes with chronic complication" towards the cumulative comorbidity score.
[4] If "mild liver disease" and "moderate or severe liver disease" are both captured during baseline period, then (of the 2 conditions) only count "moderate or severe liver disease" towards the cumulative comorbidity score.
[5] If "any malignancy (including leukemia and lymphoma)" and "metastatic solid tumor" are both captured during pre-index period, then (of the 2 conditions) only count "metastatic solid tumor" towards the cumulative comorbidity score.

Annex 2. Additional Information

List of Independent Variables for the Propensity Model

The propensity score model for the the probability of having prasugrel as the post-discharge index therapy will a wide variety of potential predictors such as:

- Index month/year
- Age or age group
- Gender
- Geographic region
- Baseline comorbidities
- Baseline medications
- Baseline clinical outcomes
- Baseline health care resource utilization
- Baseline health care resource charges
- Clinical Characteristics and Measures from Index Hospitalization

The final list of covariates to be included in the propensity score model will be provided in the SAP. All diagnoses and procedure codes will be listed in the statistical analysis plan (SAP).

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