PASS Information

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Research question and objectives	Primary objective: To compare major adverse cardiovascular events (MACE) up to one year after hospital discharge among ACS patients with no history of TIA or stroke, managed with PCI, and treated with prasugrel vs. clopidogrel. Secondary objectives: To compare demographics, baseline clinical characteristics, treatment patterns, and clinical and economic outcomes up to one year after hospital discharge among ACS patients with no history of TIA or stroke, managed with PCI, and treated with prasugrel vs. clopidogrel.
Country of study	US
Author	OptumInsight (Tanya Burton)/Lilly (Cliff Molife)

Approval Date:

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Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly and Co.
MAH contact person	Cliff Molife

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2. List of Abbreviations

Term	Definition
ACEi	Angiotensin converting-enzyme inhibitor
ACS	Acute Coronary Syndrome
ACS-PCI	ACS managed with percutaneous coronary intervention (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
CDM	Charge data master
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
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
NSTEMI	Non-ST-segment elevation myocardial infarction
OAP	Oral antiplatelet
OLS	Ordinary Least Squares
PCI	Percutaneous coronary intervention
PFT	Pulmonary function tests
PPI	Proton pump inhibitors
PRBC	Packed red blood cells
RCT	Randomized clinical trial
RX	Prescription claims data asset

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 with the post-discharge index therapy will be estimated using the proportion of days covered (PDC) during two specified time intervals: 3 months and 12 months post-discharge index therapy initiation. PDC will be calculated by dividing the total days supply of filled medications during the 3- and 12-month intervals by 90 and 365 days, respectively. 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 $\geq$ 80% will be considered adherent.

Adenosine diphosphate receptor inhibitor (ADP-ri)
ADP-ri medications are the oral antiplatelet agents: clopidogrel, prasugrel, ticagrelor, and ticlopidine.

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.

Baseline
12 months before the index hospitalization admission date.

Bleeding
Bleeding will be identified by ICD-9 diagnosis and/or procedure codes for bleeds and/or blood transfusions during medical encounters. Major/severe bleeding events will be defined by the presence of: 1) ICD-9 diagnosis and/or procedure codes for bleeding and $\geq$3 units of blood transfused (per CPT or ICD-9 procedure codes) within an inpatient hospitalization, or 2) $\geq$4 units of blood transfused (per CPT or ICD-9 procedure codes) with or without ICD-9 diagnosis and/or procedure codes for bleeding (different types of hemorrhages, epistaxis, etc.), or 3) ICD-9

diagnosis codes for intracranial hemorrhage, or 4) ICD-9 diagnosis and/or procedure codes for blood transfusions followed by death for any reason within an inpatient hospitalization.[1]

Cardiovascular (CV) events
Medical events related to clotting or emboli within the cardiovascular system.

Concomitant medications
Medications that have an overlapping days supply with the post-discharge index therapy (prasugrel or clopidogrel).

Discontinuation
Discontinuation of the post-discharge index therapy will be defined by a gap of 30 days or more in fills for the index therapy. 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[2] of last fill) ≥ 30 days
  OR
- (start date of $fill_{x+1}$) – (run-out date of $fill_x$ – 1) ≥ 30 days

The total number of fills for the post-discharge index therapy prior to discontinuation will also be calculated.

Dosing
The initial daily dose will be determined from the initial prescription and calculated based on a formula using strength, quantity, and days supply in the claims. Dose during the index hospitalization can also be captured for the subset of patients with medical chart review.

Follow-up
At least 3 months and no more than 12 months after the index hospitalization discharge date or until death, if sooner.

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

[1] Berenson K, Casciano R, Makenbaeva D, Mozaffari E, Lamerato L, Corbelli J. Economic consequences of severe bleeding in patients with acute coronary syndrome in the USA. *Adv Ther*. 2010;27(8):564-579.
[2] The run-out date will be defined as the pharmacy claim date + days supply.

- *Emergency department visits* will be defined as visits to emergency treatment centers or hospital emergency rooms during the study period
- *Ambulatory visits* will be defined as the following encounters during the study period:
  - office visits to primary or specialty care providers, urgent care clinics
  - outpatient hospitals visits
  - other ancillary settings including laboratory, radiology, and physical therapy
- *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-related Medical Encounters

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

Health Care Costs

All-cause Medical and Pharmacy Costs

Health care costs will be computed as the combined health plan and patient paid amounts for all services during the study period. Costs will be calculated for inpatient admissions, emergency department visits, ambulatory care visits (including physician office visits, outpatient hospital visits and other ancillary services), and outpatient pharmacy fills. Total costs will be calculated as the sum of all medical and pharmacy costs.

Disease-Related Medical Costs

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

Disease-Related Pharmacy Costs

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.

**Note*: All costs will be adjusted using the annual medical care component of the Consumer Price Index (CPI) to reflect inflation between study start and end dates.

Index Admission Date

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

Index Hospitalization

First hospitalization during the selection window with a primary or secondary ACS diagnosis code, PCI procedure code, and at least one claim for prasugrel or clopidogrel 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.

Index Hospitalization Treatment
The administration of ADP-ri, aspirin, and other treatments during the index hospitalization will be identified in the subset of patients with medical chart review.

Index Hospitalization Length of Stay
Total number of days during the index hospitalization, inclusive of admission and discharge dates.

ICU/CCU
An intensive care unit (ICU) or coronary care unit (CCU).

Major Adverse Cardiovascular Event(s) (MACE)
MACE is a composite endpoint of CV events that has been widely used in the CV literature[3,4] to characterize the overall efficacy or effectiveness of treatment. In this study, MACE will be defined as a composite measure based on the presence of any evidence for all-cause mortality, hospitalization for stroke, rehospitalization for myocardial infarction or unstable angina, or post-discharge revascularization (PCI or CABG).

Myocardial infarction (MI)
A cluster of events with coronary artery disease complicated by an acute intracoronary thrombus including ST elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI).

Net Adverse Clinical Event(s) (NACE)
The term NACE has been used in prior studies[4,5] to characterize the net balance for CV drugs which typically reduce MACE at the expense of increased bleeding. In this study, NACE will be defined as a composite measure based on the presence of any evidence for a MACE event, *or* hospitalization for bleeding.

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

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[3] Rao SV, Dai D, Subherwal S, Weintraub WS, Brindis RS, Messenger JC, Lopes RD, Peterson ED. Association Between Periprocedural Bleeding and Long-Term Outcomes Following Percutaneous Coronary Intervention in Older Patients. *JACC Cardiovasc Interv.* 2012; 5(9):958-65. doi: 10.1016/j.jcin.2012.05.010.
[4] Vetrovec et al. Prasugrel Compared to Ticagrelor in Acute Coronary Syndrome Patients Treated with a Percutaneous Coronary Intervention: Findings from a Large Hospital Charge Master Database. Accepted for presentation at the SCAI 2014 Scientific Sessions in Las Vegas, NV May 28-31, 2014
[5] Harjai KJ, Shenoy C, Orshaw P, Usmani S, Judy Boura J, and Mehta RH. Clinical Outcomes in Patients with the Concomitant Use of Clopidogrel and Proton Pump Inhibitors After Percutaneous Coronary Intervention: An Analysis From the Guthrie Health Off-Label Stent (GHOST) Investigators. *Circ Cardiovasc Interv.* 2011; 4:162-170. doi:10.1161/CIRCINTERVENTIONS.110.958884

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. Persistence with the post-discharge index therapy will be calculated as the number of days from the study index date to the date of discontinuation.

Post-discharge Index Therapy
The first fill for prasugrel or clopidogrel within 30 days after discharge from the index hospitalization.

Post-discharge Index Therapy Fill Date
The date of the first fill for the post-discharge index therapy.

Post-PCI length of stay
The difference in days between the PCI procedure and discharge during the index hospitalization for the subset of patients with medical chart review.

Prescriber specialty
The physician specialty on the first pharmacy claim for the post-discharge index therapy will be identified. The physician specialty on the discharge medications will be identified for the subset of patients with medical chart review.

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. The index contains 17 comorbid conditions identified using primary and secondary ICD-9 diagnosis codes during the baseline period (see Annex 1).[6,7] 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 score will be grouped into the following categories: 0-1, 2, 3, and 4+.

Rehospitalization/Readmission
An inpatient admission following the index hospitalization.

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[6] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis.* 1987; 40:373-83.

[7] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Medical Care.* 2005; 43:1130-39.

Revascularization
A coronary vessel procedure with the goal of restoring or improving perfusion to the heart following ischemia, via coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI).

Selection Window
Timeframe for identifying the index hospitalization: 01 September 2009 to 31 May 2013.

Stent thrombosis
Evidence of death or a myocardial infarction within 30 days after stenting will be considered a probable stent thrombosis (adapted from the Academic Research Consortium [ARC] definition).[8]

Study Index Date
The study index date will be defined as the discharge date of the index hospitalization.

Study Subjects
Subjects treated with prasugrel or clopidogrel within 30 days post-discharge from an ACS-PCI hospitalization.

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

Time to Post-discharge Index Therapy
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.

[8] Cutlip DE, Windecker S, Mehran R, et al.. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007 May 1;115(17):2344-51.

4. Responsible Parties

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

5. Abstract

- Title: One Year Post-discharge Clinical and Economic Outcomes among Patients with ACS Managed with PCI and Treated with Prasugrel vs. Clopidogrel

- Rationale and background: While the results from the TRITON-TIMI 38 established the superior anti-thrombotic efficacy of prasugrel in combination with aspirin over clopidogrel plus aspirin, there is currently insufficient long-term real-world data that directly compares the clinical and economic outcomes of prasugrel and clopidogrel patients. This retrospective claims database analysis supplemented with a medical chart review for a subset of patients will help to fill in this important gap in the literature.

- Research Objectives: The primary study objective is to compare major adverse cardiovascular events (MACE) up to one year of hospital discharge among ACS patients with no history of TIA or stroke, managed with PCI, and treated with prasugrel vs. clopidogrel. Secondary objectives are to compare demographics, baseline clinical characteristics, treatment patterns, and clinical and economic outcomes up to one year of hospital discharge among ACS patients with no history of TIA or stroke, managed with PCI, and treated with prasugrel vs. clopidogrel.

- Study design: Retrospective cohort study

- Population: The primary study population will include ACS patients with no history of TIA or stroke, managed with PCI, and treated with prasugrel vs. clopidogrel. Subgroups with other important characteristics (age, gender, comorbidities of interest) will be defined in the SAP.

- Variables: The primary dependent variable will be major adverse cardiovascular events (MACE) through one year of hospital discharge. Secondary dependent variables will include clinical and economic outcomes, and treatment patterns during index hospitalization and through three months and one year post-discharge from the index hospitalization. Study timeframes will be finalized in the SAP. The primary independent variable will be treatment cohort (prasugrel vs. clopidogrel) and other independent variables (covariates) will include demographics, baseline clinical characteristics, and baseline treatment utilization.

- Data sources: Optum Research Database supplemented with medical chart review for a subset of patients.

- Study size: Refer to section 9.4 for preliminary sample sizes in the Optum Research Database (ORD). Final sample size will be known 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.

6. Amendments and Updates

Not applicable.

7. 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% had diagnoses for myocardial infarction (MI), while approximately 30% were associated with unstable angina (UA).[9] 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. The use of a $P2Y_{12}$ receptor inhibitor is recommended by current treatment guidelines as a standard component of an antiplatelet regimen, generally in combination with low dose aspirin, for the follow-up treatment of patients with ACS.[10,11]

Prasugrel, a $P2Y_{12}$ 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 and managed with PCI. The TRITON-TIMI 38 trial, a randomized clinical trial (RCT) of 13,608 patients with ACS and managed with PCI (ACS-PCI), compared prasugrel to clopidogrel, both in combination with aspirin, and found that, as a more potent antiplatelet 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; hazard rate for prasugrel vs. clopidogrel: 0.81; 95% CI: 0.73-0.90; $p<0.001$).[12]

RCTs have high internal validity, and when done well, can best assess causation, or the impact of an intervention on outcomes. However, the generalizability of RCT study results to a broader patient population is often challenging due to restrictive study inclusion criteria. Retrospective claims database analyses can offer insights about the clinical and economic outcomes of a broader range of patients in usual care treatment settings, but results may be biased due to residual confounding from known and unknown factors (i.e., factors that influence both the intervention and outcome, and complicate assessments of causation).

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[9] Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics – 2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28-e292;.

[10] Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE Jr, Ettinger SM, Fesmire FM, Ganiats TG, Lincoff AM, Peterson ED, Philippides GJ, Theroux P, Wenger NK, Zidar JP. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non–ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2012;60:654 –90.

[11] O'Gara PT, Kushner FG, Ascheim DD, Casey Jr DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127:e362–e425.

[12] Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007; 357:2001-5.

TRANSLATE-ACS is an on-going observational study following more than 12,000 MI-PCI patients prospectively. This study is gathering rich clinical data through one year, but requires informed consent and relies on self-report for treatment adherence and cost outcomes. Another recent retrospective cohort study selected ACS-PCI patients on the basis of the prasugrel US prescribing information using the Premier database of hospital discharges. This study found marked differences in the profile of patients receiving prasugrel compared to clopidogrel. Prasugrel patients were younger and had a lower risk of comorbid conditions associated with bleeding. After adjustment for baseline differences, patients using prasugrel, compared to clopidogrel, had a significantly lower rate of MI-related rehospitalization with no increase in the rate of bleeding-related rehospitalization at 30 days and 90 days following the index ACS-PCI hospital discharge. The study also found that patients using prasugrel had significantly shorter length of stay and lower costs with no increased rate of bleeding during the index hospitalization. While results from this study, particularly those related to the reduction in MI, reflect the short term efficacy noted in the TRITON-TIMI 38 trial, long term observational data (> 90 days) comparing the use of these agents in the real world setting is scarce. The current retrospective claims database analysis will help fill this important gap in the literature as well as collect economic data from a large managed care health plan in the US.

8. Research Objectives

The overall hypothesis of this study is that, after adjustment for baseline differences, prasugrel will be associated with a significantly lower risk of major adverse cardiovascular events (MACE) than clopidogrel up to one year post-discharge from the index hospitalization.

8.1. Primary Objectives

1. To compare MACE with prasugrel versus clopidogrel up to one year post-discharge from the index hospitalization.

8.2. Secondary Objectives

2. To compare demographics and baseline characteristics between patients treated with prasugrel versus clopidogrel before propensity adjustment.

3. To compare index therapy treatment patterns with prasugrel versus clopidogrel including adherence, discontinuation, persistence, and switching as listed in Table 1 through 1) three months and 2) one year post-discharge from the index hospitalization.

4. To compare NACE and its components with prasugrel versus clopidogrel including bleeding as listed in Table 1 through 1) 30 days, 2) three months, and 3) one year post-discharge from the index hospitalization.

5. To compare all-cause health care resource utilization (including length of stay of the index hospitalization and subsequent readmissions) and costs with prasugrel versus clopidogrel through 1) 30 days, 2) three months, and 3) one year post-discharge from the index hospitalization. Resource utilization and costs will be stratified as listed in Table 1.

6. To compare disease-related (including MI, revascularization, stroke, unstable and stable angina, congestive heart failure, and bleeding as listed in Table 1) health care resource utilization and costs with prasugrel versus clopidogrel through 1) 30 days, 2) three months, and 3) one year post-discharge from the index hospitalization.

7. If differences in treatment patterns (i.e, adherence, persistence, switching, and discontinuation) are found, then assess factors associated with adherence, persistence, switching, and discontinuation of a) prasugrel and b) clopidogrel patients through one year post-discharge from the index hospitalization.

8. If differences in treatment patterns are found, then examine associations between treatment patterns (adherence, persistence, switching, and discontinuation) and outcomes (clinical: all-cause mortality, MACE, inpatient readmissions; economic: total costs) for a) prasugrel and b) clopidogrel patient through one year post-discharge from the index hospitalization.

8.3. Exploratory Objectives for Medical Chart Review

9. The abstracted medical chart data gathered for a subset of patients in the claims database analysis will be used to:
    - Identify new confounders not available in the claims such vital statistics (e.g., weight, smoking status) and inpatient treatment (e.g., ADP-ri, aspirin dose, CABG, type and number of stents, number of vessels)
    - Confirm the accuracy of the measured confounders in the claims including medical histories (in particular, history of TIA and stroke) and prior procedures
    - Compare the ADP-ri treatment administered during the index hospitalization to the first ADP-ri therapy identified post-discharge in the claims
    - Validate the claims-based major/severe bleeding algorithm

10. To compare stent thrombosis-related health care resource utilization through 1) three months and 2) one year post-discharge from the index hospitalization.

9. Research Methods

9.1. Study design

9.1.1. Study Overview

This will be a retrospective claims database analysis of medical data, pharmacy data, enrollment information supplemented with abstracted medical chart data for a subset of patients. This study will include data between 01 September 2008 and 31 August 2013. Study subjects will include health plan enrollees with evidence of a fill for prasugrel or clopidogrel within 30 days post-discharge from an ACS-PCI hospitalization and no prior TIA or stroke. The primary population was selected as guided by the US prescribing information for prasugrel in which patients with a history of TIA or stroke are contraindicated.[13] Of note, other patients contraindicated for prasugrel, such as those with active pathological bleeding or hypersensitivity to prasugrel or one of its components, cannot be identified in this database.

9.1.2. Claims Database Sample

9.1.2.1. *Inclusion Criteria*

The primary and secondary objectives for the study will be addressed with commercial and Medicare Advantage health plan enrollees who meet all of the following inclusion criteria and none of the exclusion criteria below:

- **ACS-PCI Hospitalization**: At least one inpatient (IP) hospitalization with primary or secondary ACS diagnosis codes *and* PCI or coronary stent procedure codes between 01 September 2009[14] 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.
  - The ***study index date*** will be defined as the discharge date of the first such ACS-PCI hospitalization.
- **ADP-ri Index Fill**: At least one outpatient pharmacy fill for prasugrel or clopidogrel between the study index date and 30 days post-discharge from the index hospitalization.
  Note:
  - 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 *post-discharge index therapy.*
- **Age**: Aged ≥18 years as of the study index date.

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[13] Effient [package insert]. Indianapolis, IN: Eli Lilly and Company; 2013.
[14] Prasugrel was approved by the FDA in July 2009.

- **Continuous Enrollment**: Continuously enrolled in a commercial or Medicare Advantage health plan with medical and pharmacy benefits for 12 months before the index admission date (baseline) and for at least 3 months after the index hospitalization discharge date (i.e., the study index date) or until death, if sooner (follow-up).

9.1.2.2. *Exclusion Criteria*

- **Multiple ADP-ri**: Pharmacy fills for more than one ADP-ri (prasugrel, clopidogrel, ticagrelor, ticlopidine) within 30 days following the index discharge date.
- **Any history of TIA or stroke**: Any medical claims for TIA or stroke prior to or during index hospitalization

9.1.3. Cohort Assignment

Subjects will be assigned to one of two mutually exclusive cohorts based on the post-discharge index therapy (prasugrel or clopidogrel).

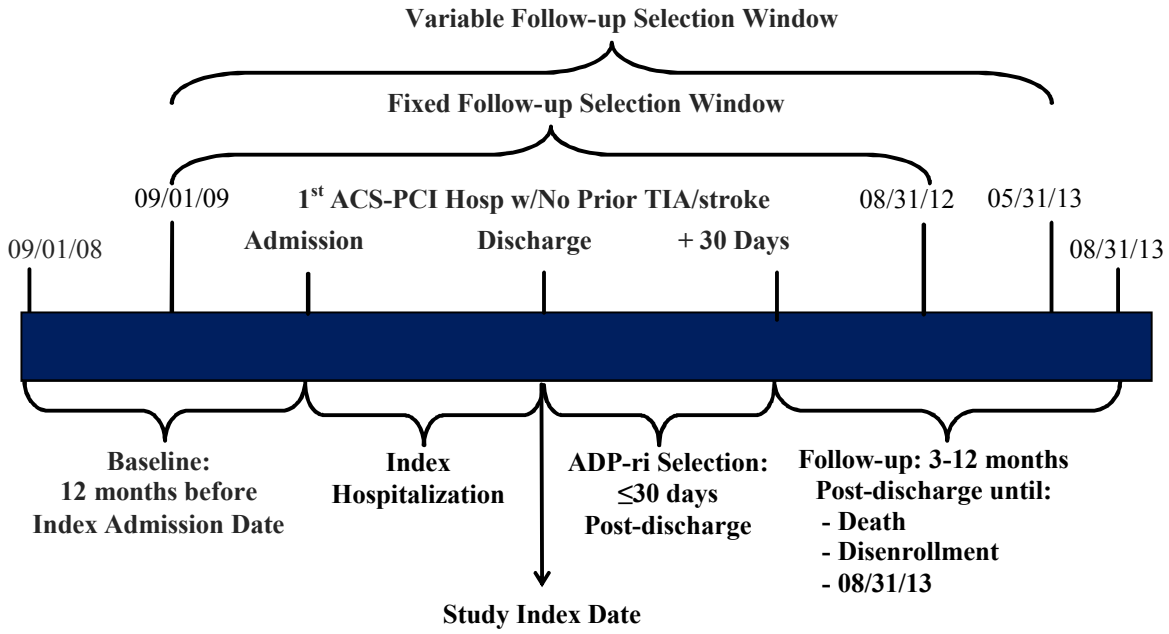
9.1.4. Study Timeframe

Five observation periods will be defined:

1. **Index hospitalization period**: Days between, and including, the admission and discharge dates of the index hospitalization.
2. **Baseline period**: 12 months before the index hospitalization admission date.
3. **ADP-ri index selection period**: Study index date to 30 days post-discharge from the index hospitalization.
4. **Variable follow-up period**: Days on and after the study index date until 3 or more months after the study index date or until death, if sooner. Maximum follow-up will be 12 months.
5. **Fixed follow-up period**: Days on and after the study index date until 12 months after the study index period or until death, if sooner. This one year follow-up period will be used to assess the primary endpoint as a secondary objective, adherence, persistence, and costs.

Figure 1 illustrates the study timeframe.

Figure 1. Study Timeframe



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

Baseline characteristics and clinical and economic outcomes between prasugrel and clopidogrel patients will be examined for the following subgroups:

1. <75 years of age OR ≥75 years of age with prior MI or diabetes*
2. Index admission diagnosis (STEMI, NSTEMI, UA)
3. Gender (Male vs. Female)

* Subgroup #1 was selected to reflect the US prescribing information for prasugrel in which patients with a history of TIA or stroke are contraindicated, and patients ≥75 years of age are generally not recommended for prasugrel use, except in high-risk situations, such as patients with diabetes or a history of prior MI.[13]

9.1.6. Medical Chart Review Sample

The objectives for the medical chart review as described in Section 8.3 will be addressed by abstracting medical chart data for a subset of ACS-PCI patients with no evidence of TIA or stroke in the claims during baseline or the index hospitalization. In addition, the medical chart sample will be limited to commercial health plan enrollees, as medical chart abstraction is not allowed by Federal law for Medicare Advantage health plan enrollees. An oversample of 3,600 study subjects in the claims database analysis will be identified in order to obtain a final sample of 1,200 completed charts, or 600 per cohort. The hospital or medical facility where each index ACS-PCI hospitalization took place will be identified and contacted to arrange medical chart review. The final sample will be a convenience sample of commercial study subjects with facilities willing to participate in the medical chart abstraction process. True

representativeness cannot be guaranteed due to the voluntary nature of the chart review process. Abstracted medical chart data will be linked to the administrative claims data for analysis.

9.2. Variables

Table 1. Study Variables by Study Objectives and Data Source

OBJECTIVE	VARIABLE	DEFINITION	CLAIMS	CHART
1, 4, 5, 10	Index hospitalization bleeding	Bleeding during the index hospitalization (n, %) - Any bleeding - Any transfusion of WB, PRBC, or platelets - Major/severe (*claims algorithm)	Y*	Y
		- Periprocedural (24-48 hours after PCI)	N	Y
	Index hospitalization stroke	Any evidence of a stroke occurring during the index hospitalization on the medical chart (n, %)	N	Y
	Post-discharge bleeding	Transfusion or intracranial hemorrhage bleeding during 30 days, 3 months and 1 year post-discharge from the index hospitalization (n, %)	Y	N
		Major/severe bleed (*algorithm)	Y*	N
		Days to first bleed (mean, SD, median)	Y	N
	Post-discharge disease-related events	Evidence of other CV events such as MI, revascularization, stroke, unstable and stable angina, and congestive heart failure during 1 year post-discharge from the index hospitalization (n, %)	Y	N
	Post-discharge MACE	Composite and individual measures of MACE 30 days, 3 months and 1 year post-discharge from the index hospitalization (n, %):		
		- All-cause mortality	Y	N
		- Hospitalization for MI (NSTEMI, STEMI)	Y	N
		- Hospitalization for unstable angina (UA)	Y	N
		- Hospitalization for stroke	Y	N
		- Revascularization (PCI, CABG)	Y	N
		Days to the first occurrence of each event (mean, SD, median)	Y	N
	Post-discharge NACE	MACE or evidence of hospitalization for bleeding during 30 days, 3 months and 1 year post-discharge from the index hospitalization (n, %)	Y	N
	Post-discharge other Composite	Composite of all-cause mortality, hospitalization for stroke, or rehospitalization for MI (n, %)	Y	N
	Post-discharge stent thrombosis	Stent thrombosis (*algorithm)	Y*	N
2	Age	As of the study index date (n, %, mean, SD, median years) - 18-44, 45-54, 55-64, 65-74, ≥75	Y	N
	Comorbidities/ Medical history	Baseline comorbidities (n, %) - Arterial embolism, Asthma, Atrial fibrillation, Cardiac dysrhythmia, Cardiomyopathy, Cerebrovascular disease, Chronic Obstructive Pulmonary Disease (COPD), Deep venous thrombosis, Diabetes, Dyslipidemia, Dyspnea, Congestive Heart Failure (CHF), Hemorrhagic tendencies of blood dyscrasia, History of bleeding, Hypertension, Hypotension, Ischemic Heart Disease, other than ACS (MI or UA), TIA, Liver disease, Obesity, Osteoarthritis, Peripheral vascular disease, Phlebitis, Pulmonary embolism, Renal impairment (Renal failure, Chronic Kidney Disease (CKD), Other renal insufficiency), Rheumatoid Arthritis, Sepsis, Stroke (Hemorrhagic stroke, Ischemic stroke, Unspecified stroke), Thyrotoxicosis, thrombocytopenia, peptic ulcer disease (n, %)	Y	Y
		Quan-Charlson Comorbidity Index (n, %, mean, SD, median) - 0-1, 2, 3, 4+	Y	N
	Health care resource utilization	All-cause medical encounters during baseline (n, %, mean, SD, median) - Inpatient admissions - Length of inpatient stays	Y	N

OBJECTIVE	VARIABLE	DEFINITION	CLAIMS	CHART
		- Outpatient visits (physician and outpatient hospital visits) - Other medical encounters		
	Health care resource costs	All-cause costs during baseline (mean, SD, median) - Total (medical + pharmacy costs) - Medical costs - Inpatient costs - Emergency department costs - Outpatient costs - Pharmacy costs	Y	N
	Health plan region	US Census geographic regions (n, %) - Northeast, Midwest, South, West	Y	N
	Index year	Year of the index hospitalization admission date	Y	Y
	Insurance type	Commercial, Medicare Advantage (n, %)	Y	N
	Primary payer type	HMO, PPO, POS, Other (n, %)	Y	N
	Prior MI	Yes, No (n, %)	Y	Y
	Prior revascularization	CABG, PCI (n, %)	Y	Y
	Sex	Male, Female (n, %)	Y	Y
	Smoking status	Yes, No (n, %)	N	Y
	Socioeconomic status (SES)	Race/ethnicity (n, %) - Caucasian, African American, Hispanic, Asian, Other	Y	Y
		Income/Net worth (mean, SD, median)	Y	N
	Treatment utilization	Baseline medication use (n, %) - ADP-ri (clopidogrel, prasugrel, ticagrelor, ticlopidine), phosphodiesterase inhibitor (cilostazol), HMG CoA reductase inhibitors (statins), proton pump inhibitors, antihypertensives (major class), antidiabetes medications (major class)	Y	N
	Weight	Lbs/kg (mean, SD, median)	Y	Y
3	Post-discharge adherence	Proportion of days covered (PDC) for index therapy (n, % mean, SD, median) during 3 months and 1 year post-discharge from the index hospitalization: - <20%, 20-<40%, 40-<60%, ≥80, <80%	Y	N
	Post-discharge discontinuation	Stop or gap in index therapy fills during 3 months and 1 year post-discharge from the index hospitalization (n, %)	Y	N
	Post-discharge index dosing	Daily dose of index therapy on the post-discharge index therapy fill date (mean, SD, median dose)	Y	N
	Post-discharge index fills	Total number of fills for the index therapy during 3 months and 1 year post-discharge from the index hospitalization (mean, SD; median)	Y	N
	Post-discharge index switch	Switch to an ADP-ri different than the post-discharge index therapy during 3 months and 1 year post-discharge from the index hospitalization (n, %)	Y	N
		Days to first switch from post-discharge index therapy(mean, SD, median)	Y	N
	Post-discharge index therapy	First fill for clopidogrel or prasugrel within 30 days post-discharge from the index hospitalization and time to first fill after discharge from the index hospitalization	Y	N
	Post-discharge index therapy copay	Patient-paid copays for index therapy during 3 months and 1 year post-discharge from the index hospitalization, standardized to 30 days supply (mean, SD, median)	Y	N
	Prescriber specialty	Prescriber specialty for post-discharge index therapy on index therapy fill date (n, %) - Family/General Practice, Cardiology, Emergency Medicine, Endocrinology, Other	Y	Y
	Post-discharge persistence	Days to discontinuation (mean, SD, median)	Y	N
	Post-discharge treatment duration	Days from first fill to last fill of post-discharge index therapy (mean, SD, median)	Y	N

OBJECTIVE	VARIABLE	DEFINITION	CLAIMS	CHART
	Number of unique post-discharge medications	Total number of unique medications within 30 days post-discharge from the index hospitalization (mean, SD; median)	Y	N
	Post-discharge concomitant medications	Concomitant medication during 30 days, 3 months, and 1 year post-discharge from the index hospitalization (n, %): - - ADP-ri (clopidogrel, prasugrel, ticagrelor, ticlopidine), phosphodiesterase inhibitor (cilostazol), HMG CoA reductase inhibitors (statins), proton pump inhibitors, antihypertensives (major class), antidiabetes medications (major class)	Y	N
6, 7	Post-discharge resource utilization	PPPM number of all-cause and disease-related health care utilization during one year post-discharge from the index hospitalization (n, %, mean, SD, median) - Inpatient admissions - Length of stays - ICU/CCU stays - Length of ICU/CCU stays - Outpatient hospital visits - Physician office visits - Family/general practice - Cardiology - Endocrinology - Other specialties - Emergency department visits - Other medical encounters	Y	N
	Post-discharge resource costs	PPPM all-cause and disease-related costs (mean, SD, median) during one year post-discharge from the index hospitalization: - Total (medical + pharmacy costs) - Medical costs - Inpatient costs - Emergency department costs - Outpatient hospital costs - Physician office visits - Family/general practice - Cardiology - Endocrinology - Other specialties - Other medical encounters - - Pharmacy costs - ADP-ri costs	Y	N
10 (See Medical Chart Abstraction Form for complete list of index hospitalization variables)	Index hospitalization revascularization	PCI procedure during the index hospitalization (n, %)	Y	Y
		Stent implantation (n, %) - DES, BMS, unknown, none	Y	Y
		Number of stents (n, %) - 1, 2, 3, 4+	Y	Y
		Number of vessels (n, %) - 1, 2, 3, 4+	Y	Y
		CABG during the index hospitalization (n, %)	Y	Y
		Days post-PCI to discharge from the index hospitalization admission (mean, SD, median)	N	Y
	Index hospitalization	ACS diagnosis during the index hospitalization (n, %) - STEMI, NSTEMI, UA	Y	Y
		Days during index hospitalization (mean, SD; median)	Y	Y
		Days during ICU/CCU index hospitalization (mean, SD; median)	N	Y
		Days to index therapy initiation relative to index admission date and PCI (mean, SD, median)	N	Y
		Initial and discharge dose amounts of prasugrel and clopidogrel % with loading dose	N	Y
		Hospital characteristics (n, %, mean, SD, median)	Y	N

OBJECTIVE	VARIABLE	DEFINITION	CLAIMS	CHART
		- urban/rural		
		Medications administered during the index hospitalization (n, %) - ADP-ri, aspirin, glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban), fibrinolytic therapy, anticoagulant (unfractionated heparin, LMWH (dalteparin, enoxaparin, tinzaparin), fondaparinux), direct thrombin inhibitor (bivalirudin), other anticoagulant or antithrombin (rivaroxaban, dibigatran, apixaban, coumadin)	N	Y
		- Persistence with initial inpatient therapy on the discharge date	N	Y

9.3. Data sources

9.3.1. Optum Research Database (ORD)

Commercial Claims Data

Optum has access to a proprietary research database containing medical and pharmacy claims with linked enrollment information with data covering the period from 1993 to current. For 2011, data relating to approximately 12.8 million (actual=12,818,738) individuals with both medical and pharmacy benefit coverage are available. An additional 10.4 million (actual=10,424,191) enrollees with medical benefits only are available. Underlying information is geographically diverse across the United States and fairly representative of the U.S. population. Of the 12.8 million individuals, race/ethnicity and financial resource information was available for approximately 75-85 percent of the individuals.

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The claims history is a profile of all outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications.

Medical claims or encounter data are collected from all available health care sites (inpatient hospital, outpatient hospital, ER, physician's office, surgery center, etc.) for virtually all types of provided services, including specialty, preventive and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers, e.g., physicians, use the Health Care Financing Administration (HCFA)-1500 or Centers for Medicare and Medicaid Services (CMS)-1500 formats. Claims for facility services submitted by institutions, e.g., hospitals, use the Uniform Billing (UB)-82, UB-92, UB-04, or CMS-1450 formats. Medical claims include: multiple diagnosis codes recorded with the ICD-9-CM diagnosis codes; procedures recorded with ICD-9-CM procedure codes, Current Procedural Terminology (CPT), or Healthcare Common Procedure Coding System (HCPCS) codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include medications dispensed in hospital. Approximately six months following the delivery of services is required for complete medical data.

Pharmacy claims are typically added to the research database within six weeks of dispensing. Approximately six months following the delivery of services are required for complete medical data.

Medicare Advantage and Part D Data

Medical and pharmacy claims data are available for approximately 3.6 million enrollees since 2006 that are enrolled in Medicare Part C (commonly referred to as the Medicare Advantage program) through an offering associated with Optum. Prior to 2006, data were available for approximately 500,000 of these enrollees. In addition, approximately five million enrollees in a Medicare Part D benefit have pharmacy claims data available for each year since the start of the program in 2006. Medicare Advantage enrollees choose to receive all of their health care services through a provider organization in lieu of Medicare Part A/B coverage (commonly referred to as Medicare Fee for Service).

There are certain limitations related to pharmacy claims for the Medicare Advantage population prior to 2006. Prior to 2006, managed Medicare enrollees in the plans affiliated with Optum had pharmacy coverage through their health plan—one of the benefits of enrollment in a managed Medicare plan. For approximately 25 percent of these enrollees, these pharmacy benefits had caps on expenditures. Enrollees with substantial pharmacy expenditures may have exceeded their cap in certain years. For these members, in most cases, it is expected that additional filled prescriptions will not be observed in the claims data.

Beginning in 2006, complete medical and pharmacy information is available for Medicare enrollees with medical and Part D coverage (MAPD). Pharmacy claims contain sufficient information to trace patients' pharmacy expenditures through the multiple phases of the Part D plans.

9.3.2. Mortality Data

By linking external mortality data to ORD, it is possible to determine the timing of deaths that are not otherwise captured in the claims. After subjects are linked, these data can be used to inform sample selection. That is, subjects 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. Mortality data can also be used to modify outcomes and other study endpoints.

Mortality information is sourced from the SSA death files. The SSA files, with a proper linkage, allow establishment of the date of death. They do not, however, include information on cause of death. Month and year of death are available for individuals 18 years of age and older only. Approval through the Optum data disclosure analysis process is required for the use of the exact date of death (month, day, and year) and requires an additional processing fee.

9.3.3. Socioeconomic Status Data

In addition, to allow for more powerful insight into prevalence and burden of illness, Optum has a unique source of individual-level data which can be linked to ORD that allows for analysis of socioeconomic characteristics. Specifically, these data elements include race/ethnicity, language preference, occupation, household income category, and household

net worth category. The data populating these socioeconomic elements are generated by a combination of self-report, modeling, census data, and a variety of other individual-level and population-level data sources. Certain data elements may be missing for some individuals in the claims database. The most complete variables such as race/ethnicity and income category are populated for approximately 75-80 percent of patients. These data have been used extensively in market analyses and population segmentation analyses. While these data have application to health economics and outcomes research, certain limitations are associated with these data, including inaccuracy in assignment of socioeconomic status, missing data, and pre-defined categorizations (e.g., income level).

9.3.4. Medical Chart Data

The claims database analysis will be supplemented with abstracted medical chart data for a subset of study subjects. The medical chart data will come from a medical chart review of patients identified explicitly for this study from the administrative claims research database, following receipt of the appropriate approvals. The hospital or medical facility where each index ACS-PCI hospitalization took place will be identified using the administrative claims data. The facility most relevant for the study will be identified for each patient. Facilities will be invited to participate in the study and contacted to make arrangements for the medical chart review.

Because study subjects will be selected from ORD, the study concept and any communication with health care providers must be approved by the large U.S. health plan affiliated with Optum. Optum will submit a study synopsis and network physician study-related communication materials to the health plan for review. Following health plan approval, the study will be submitted for institutional review board (IRB) and privacy board review. Optum will communicate directly with the IRB and privacy board to address any questions and/or provide any additional information in connection with the reviews. Lilly shall provide any necessary assistance or documents required for the submission to the IRB and privacy board. Approval from an IRB or privacy board for this study is not guaranteed. Optum will initiate medical chart abstraction activities only after the study protocol and study documents have been approved and Optum is granted a Waiver of Authorization by the privacy board and a waiver of the informed consent requirement by the IRB. Upon receipt of the Waiver of Authorization from privacy board, Optum will provide a copy of the waiver document and general study information to the relevant data sources for approval to utilize such data source's data in the study, which is not guaranteed.

Following health plan, IRB, and privacy board approvals, Optum will send a research study notification letter to the health plan market medical directors (MMDs) to alert them of a medical chart review study being conducted in the field. The MMDs will each receive an email containing a study synopsis, a copy of the network physician abstraction request letter, and a list of providers/medical facilities that will be contacted for participation in their market. Upon completion of the study, Optum will share published study results with the MMDs.

9.4. Study size

The following sample size and power calculations are for the claims database analysis, the primary data source for this study. The subset of patients selected for chart abstraction (medical chart review) will not provide adequate statistical power for outcomes comparisons.

Table 2 provides preliminary sample sizes available in the Optum Research Database for commercial and Medicare Advantage health plan enrollees between July 1, 2009 and June 30, 2013 with the following study criteria: 1) at least one ACS hospitalization, 2) at least one ACS hospitalization with PCI procedure codes during the same hospitalization, 3) at least one ACS-PCI hospitalization with a fill for prasugrel or clopidogrel within 30 days post-discharge, 4) continuously enrolled for 12 months before the admission date and six month after discharge from the ACS-PCI-ADP hospitalization, and 5) with no baseline TIA or stroke were identified (n=27,284). Among these, 5,101 (19%) had at least one fill for prasugrel, 21,548 (79%) had at least one fill for clopidogrel, and 635 (2%) had at least one fill for prasugrel and clopidogrel within 30 days post-discharge the ACS-PCI hospitalization.

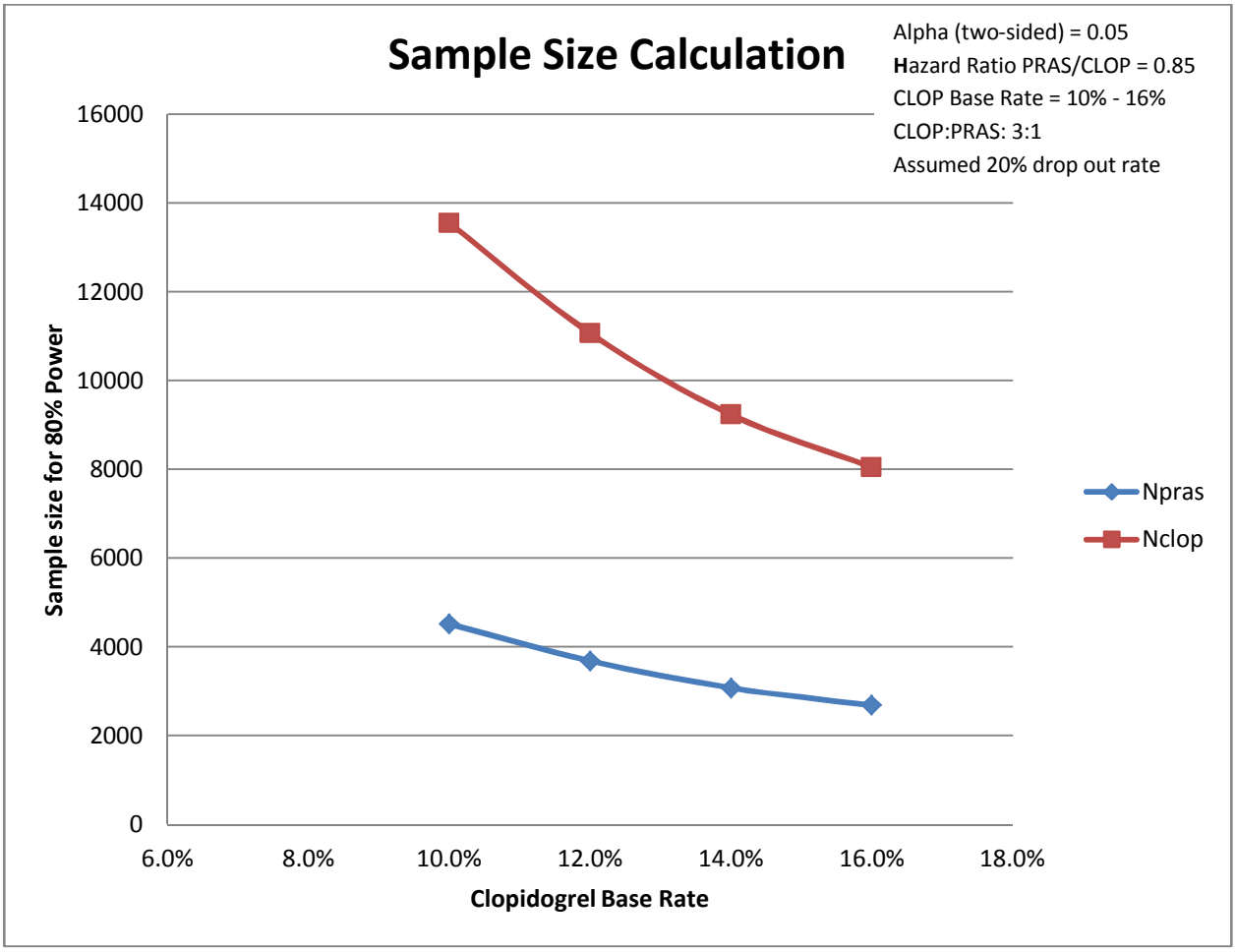
Table 2. Number of Patients Available for Analysis (July 1, 2009 – June 30, 2013)

Steps	Subset of Step	Criteria	Count
1	ACS + PCI + ADP-ri + CE + no TIA/stroke	At least one inpatient hospitalization with ACS diagnosis codes in the primary or secondary position *plus* PCI procedures codes *plus* At least one fill for prasugrel or clopidogrel within 30 days post-discharge from the ACS-PCI hospitalization *plus* Continuously enrolled at least **365** days before the admission and **180** days after discharge from the ACS-PCI-ADP hospitalization *plus* No baseline TIA/stroke	27,284
		- Prasugrel	5,101
		- Clopidogrel	21,548
		- Prasugrel and clopidogrel	635

These counts are for informational purposes only and may not represent the actual number of enrollees available for analysis. Application of other selection criteria required for this study or other factors may further reduce the available sample size. However, for the primary population, ACS-PCI patients with no history of TIA or stroke, treated with prasugrel or clopidogrel post-discharge from the index hospitalization (Table 2), the above sample sizes will provide 92% power at a 0.05 two-sided significance level to detect a 15% reduction in the adjusted hazard ratio (HR=0.85), assuming a clopidogrel base rate of 12% for MACE up to one year after the index hospitalization discharge and a 3:1 clopidogrel to prasugrel ratio. Of note, the study power

will vary as a function of both the clopidogrel event rates (as shown in Figure 2) and the magnitude of the treatment effect.

Figure 2. Sample Size Calculation for 80% Power



9.5. Data management

Datasets and analytic programs will be exclusively maintained, accessed, and analyzed by researchers at Optum. No patient level data will be transferred to the study sponsors. All data will be stored according to Optum's procedures.

9.6. Data analysis

9.6.1. Missing Data

No imputation of missing data will be conducted for outcome variables. For covariates, missing data may be addressed through methods such as creation of missing data categories (for categorical variables). This will be done to avoid selection bias that can occur by deleting cases with missing variables of interest. Details will be provided in the statistical analysis

plan. Sensitivity analysis may be considered if the amount of missing data is substantial (>20%).

9.6.2. 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, and max for continuous variables. Differences between cohorts will be assessed using Chi-square test for categorical variables and t-test and ANOVA for continuous variables. Exact tests, bootstrapping and/or nonparametric tests will be used as appropriate. All tests will be two-sided.

9.6.3. Unadjusted Outcomes 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), survival (time to death), and time to first occurrence of a major adverse cardiovascular event.

9.6.4. Propensity Score Creation

The propensity score adjustment methodology has been widely used in observational studies for causal inference ever since it was introduced by Rosenbaum and Rubin in 1983.[15] Propensity score matching will be the primary analysis. However, if propensity score matching cannot produce balanced matched cohorts with at least 90% of the prasugrel sample, then propensity score stratification will be considered.

Propensity score matching

Matching on propensity score can achieve a very high degree of balance between comparison groups and therefore, can mitigate confounding by baseline characteristics that may independently affect outcomes of interest. A propensity score for each subject will be defined as the probability of being in the prasugrel cohort and estimated using logistic regression. Prasugrel and clopidogrel subjects may be matched on their propensity scores using a greedy or optimal method to adjust for potential confounding bias.[16,17]

The first step in the primary (propensity adjusted) analysis will 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 and baseline treatment utilization measures as the independent variables in the

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[15] Rosenbaum PR and Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 70(1):41–55, 1983.

[16] Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984; 79:516-24.

[17] Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. Stat Med 2007; 26:20-36.

model. These independent variables will be selected *a priori* based on literature and expert opinion as potential confounds (i.e., factors related to both cohort and outcome).[18,19,20,21,22,23,24] The final list of independent variables to be included in the propensity score model will be determined following review of the baseline descriptive statistics. 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 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.

If using greedy or optimal matching, prasugrel and clopidogrel subjects will be matched 1:1-1:3.[25] Subjects not matched may be excluded from analysis. The success of the matching procedure will be evaluated by comparing the post-matched characteristics included in the propensity score model. Model modifications may be needed to increase sample size or

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[18] Bae JP, Ernst FR, Lipkin C, et al. Hospitalization Costs of Acute Coronary Syndrome Patients Undergoing Percutaneous Coronary Intervention: A Comparison Between Clopidogrel and Prasugrel Patients in a US Hospital Database. Abstract 730. 2012 Transcatheter Cardiovascular Therapeutics Annual Meeting, Miami, FL.

[19] Bae JP, Faries DE, Ernest FR et al. Assessment of 30-Day Rehospitalization for Acute Myocardial Infarction in Patients with Acute Coronary Syndrome Who Received Percutaneous Coronary Intervention: A Comparative Effectiveness Study of Clopidogrel and Prasugrel. Abstract TCT-53. 2012 Transcatheter Cardiovascular Therapeutics Annual Meeting, Miami, FL.

[20] Cohen, M. Predictors of bleeding risk and long-term mortality in patients with acute coronary syndromes. *CMRO*. 2005;21(3): 439–445.

[21] Moscucci M, Fox KA, Cannon CP, Klein W, Lopez-Sendon J, Montalescot G, White K, Goldberg RJ, Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J.* 2003;24:1815-1823.

[22] Mehran R, Pocock SJ, Stone GW, Clayton TC, Dangas GD, Feit F, Manoukian SV, Nikolsky E, Lansky AJ, Kirtane AJ, White HD, Colombo A, Ware JH, Moses JW, Ohman EM. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. *Eur Heart J*. 2009;30:1457–1466.

[23] Bae J, Ernst FR, Lipkin C, Faries DE, Zhao Z, Moretz C. Hospital length of stay after PCI among ACS patients treated with clopidogrel or prasugrel in a US hospital database [Abstract]. American Hospital Association Quality of Care and Outcomes Research (AHA QCOR), Atlanta, GA, May 2012.

[24] Ernst FR, Bae J, Lipkin C, Faries DE, Zhao Z, Moretz C. A comparison of bleeding in patients treated with clopidogrel or prasugrel in a US hospital database [Abstract]. American Hospital Association Quality of Care and Outcomes Research (AHA QCOR), Atlanta, GA, May 2012.

improve balance between the cohorts. Descriptive analysis comparing matched and unmatched subjects will also be provided.

Propensity Score Stratification
If the final matched sample size does not meet the aforementioned criterion, then propensity score stratification will be used. Propensity score stratification method has been reported to eliminate 85% to 90% of the treatment bias in observational cohorts. 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 and assumptions of the propensity score adjustment (matching or stratification) will be evaluated (e.g., using significance testing, assessment of standardized differences, and side-by-side boxplots or histograms).[26] As a rule of thumb, standardized differences greater than 0.10 indicate imbalance that may require further investigation.[27] The propensity model will be finalized prior to initiating analysis of the outcome measures.

9.6.5. Propensity-Adjusted Outcomes Analyses

9.6.5.1. Analysis of Categorical Outcomes

Categorical outcomes variables associated with the secondary objectives including rates of rehospitalization (disease-related and all-cause), bleeding, switching, discontinuation, and all-cause mortality may be assessed as follows: If propensity score matching method is implemented, the correlation for paired sample will be considered in the statistical methods. However if propensity score stratification method is implemented, PROC GENMOD model controlling the propensity score strata may be applied. The interaction between propensity score strata and the treatment will also be examined. If the interaction term turns out to be significant, the relative risk in each stratum will be outputted to examine the variability across the strata.

Cohort differences will be summarized using both the estimated relative risk and risk differences from this model. 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).

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[26] Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: A Monte Carlo study. *Statistics in Medicine*. 2007;26:734–753. doi: 10.1002/sim.2580

[27] Austin PC, Mamdani MM. A comparison of propensity score methods: A case-study estimating the effectiveness of post-AMI statin use. *Statistics in Medicine*. 2006;25:2084–2106. doi: 10.1002/sim.2328

9.6.5.2. Analysis of Continuous Outcomes

Primary objective: One year MACE

In addition to KM curves, multivariate Cox proportional hazards models will be used to assess the primary objective using an *on treatment* approach where patients will be censored at the end of treatment exposure time window (time of discontinuation or switching) and not allowed to switch treatment groups on the basis of their treatment use. If high rates of switching and/or discontinuation (threshold will be specified in the SAP) are observed, then an *as treated* analysis, where patients will be censored at the end of treatment exposure time window but allowed to switch treatment groups on the basis of their treatment use, may be conducted as a secondary analysis. Time-varying treatment exposure and treatment status as a time-dependent covariate may be incorporated into the Cox proportional regression model(s) as appropriate. In addition, an approach where patients will be assigned to the treatment they are first exposed (based on first prescription fill post index hospitalization discharge), regardless of discontinuation or switching, will be used to assess the primary endpoint (up to one year MACE) as a secondary objective.

Secondary objectives:

1. Time to Event Endpoint

Multivariate Cox proportional hazards models will also be used to compare secondary outcomes including time to MACE, NACE, all-cause mortality, and treatment patterns (e.g., time to first fill, persistence) between study cohorts. (Additional model details will be provided in the SAP).

2. Resource Utilization, Costs, and Treatment Patterns

Cohort differences in continuous outcome variables will be analyzed using appropriate regression models based on the distribution of the study outcome. Medical costs will be modeled using generalized linear models (GLM) with a gamma specification and log link. Resource utilization outcomes (e.g., LOS, number of fills,) will be modeled using ordinary least squares (OLS) regression. Counts of resource utilization and adherence (e.g., number of hospital admissions, PDC≥80%) will be analyzed using logistic regression or negative binomial, depending on the frequency of events. Treatment cohort (prasugrel or clopidogrel), propensity score strata, and the cohort-by-propensity score strata interaction term will be included as independent variables in the models. Least squares means and 95% confidence intervals will be estimated on the difference in mean costs. Alternative and more appropriate models may be employed after assessment of the observed distribution of continuous dependent variables and prior to any outcomes analyses.

Multicolinearity and interaction between independent variables for all afore mentioned regression models will be examined and addressed as appropriate. A p-value <0.05 will be considered statistically significant with no adjustment for multiple comparisons. All analyses will be based on observed, not projected, data. All analyses will be conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC). The Benjamini-Hochberg method[28] may be used

[28] Benjamini, Y. and Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society*, Series B, 57, 289-300.

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.

9.6.6. 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 blood pressure), a sensitivity analysis will be conducted using the rule-out method.[29]

   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.

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 costs.[30] Therefore, CLT-based methods (ANCOVA or traditional OLS models) may be used as a sensitivity analysis of costs and other continuous dependent variables. Multivariate logistic regression without propensity adjustment 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.

   Note: If propensity score matching is used for adjustment in the primary analysis, then sensitivity analyses may include the use of 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 the use of the same propensity model with a different outcomes model OR a regression model without propensity adjustment.

3. Sensitivity analyses may also be conducted to assess generalizability of the results using the primary methods/models but:

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[29] Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. pharmacoepidemiology and drug safety 2006; 15: 291–303.

[30] Lumley T, Diehr P, Emerson S, and Chen L. The Importance of the Normality Assumption in Large Public Health Datasets. *Annu. Rev. Public Health*. 2002, 23:151–69. DOI: 10.1146/annurev.publheath.23.100901.140546

a) Define disease-related medical encounters and costs using a *primary* diagnosis of any disease-related event instead of *primary or secondary* diagnosis,
b) Exclude patients with prior use of the index therapy (i.e., with pill coverage within 6 month prior to index hospitalization admission),
c) Define discontinuation as medication gap ≥ 60 days,
d) Use 70% and 90% as adherence cut-offs instead of 80%,
e) Include patients with fills for both prasugrel and clopidogrel within 30 days post-discharge the index hospitalization and consider the most recent qualifying fill as the index therapy,
f) Examine outcomes before and after the release of generic clopidogrel in May 2012,
g) Not counting patients who switch to another OAP (except aspirin) as discontinuations,
h) Examine outcomes among patients with less than 12 months of continuous enrollment.
i) Explore level of agreement between medical charts and claims data for:
    - Medical histories, in particular, history of TIA and stroke (if evidence of TIA or stroke are found in the charts when none is expected in the claims, then accuracy of the patient selection criteria will be revisited/reconsidered)
    - Inpatient versus outpatient ADP-ri drug use (if the switch rate is high, then validity of in-hospital outcomes using claims data will be revisited/reconsidered)

9.7. Quality control

The approach Optum takes in its research is geared toward the highest quality of scientific rigor and accurate, quality results. In particular, Optum focuses on quality at each step of the process.

- Optum always strives to develop a study approach that is of sound scientific design and meets clinically rigorous review. To address the important research questions, Optum develops a detailed study protocol that includes definitions, codes, analyses, and table shells for the study. A member of the Optum clinical team is involved in reviewing the appropriateness and validity of the coding strategy and in identifying any issues that may be relevant but were not discussed in the proposal phase of the project. The protocol further provides Optum and the client an opportunity to solidify the research questions and to address any potential gaps in information.

- A study is only as good as the data set created for analysis. To generate the most accurate data set, Optum incorporates rigorous quality assurance checks during data set construction. Several checks are used, including record-level verification of all data elements, double programming of certain portions of the data set, programming data edit checks, visual review of raw claims data against the constructed data elements, and review of analysis to assess validity of results.

- Analysis is performed by a statistician or senior analyst under the supervision of the project director. The project director reviews output for consistency with the analysis plan, for quality, and for accuracy. Further, results are reviewed with the client to establish that the results meet the client's expectations.

- The final deliverables produced by Optum receive internal review by a clinical consultant and/or by another senior researcher for quality and completeness

- In addition to the internal quality processes, Optum has specific internal standard operating procedures (SOPs) that have been approved and are monitored by the Optum organization. The SOPs include:

  - Protocol Development for Health Economic and Outcomes Studies
  - Study Reports for Health Economic and Outcomes Studies
  - Health Economics and Outcomes Analytic Data Creation and Verification for Outcomes Studies Utilizing Administrative Claims Data
  - Health Economics and Outcomes Research Archiving

9.8. Limitations of the research methods

Limitations of this study include those inherent in any retrospective cohort studies using administrative claims.

- 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.
- 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.
- ORD includes outpatient pharmacy claims only, which means the treatment patients received during their index hospitalization will be unknown. As a result, the first treatment observed within 30 days post-discharge will be assumed to be the same treatment initiated during the index hospitalization. This assumption will be checked for the subset of patients with medical chart review.
- 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 not persistent may suggest that the patient failed to take the product as directed even though the patient followed the directions appropriately.
- Health care received outside the health insurance plan will not appear in the claims data.
- Over-the-counter medications, such as aspirin, are not captured in the pharmacy database.
- Several potential confounders, including socioeconomic status and body mass index or weight 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 in the claims data source. However, the medical chart review and the addition of the socioeconomic database will enhance identification and measurement of important confounders.
- Data entry errors may exist at the site of care. The medical chart review will enhance identification and measurement of study variables.
- While post-discharge PCI is a component of the primary MACE endpoint, it cannot be determined using administrative claims whether the PCI was planned or clinically driven.

Planned follow-up PCI should not be affected by use of prasugrel or clopidogrel and, therefore, may underestimate a potential benefit of prasugrel on reducing clinically driven PCI. However, both planned and unplanned post-discharge PCI do have resource utilization implications.

9.9. Other aspects

Not applicable.

10. Protection of Human Subjects

No subject's identity or medical records will be disclosed for the purposes of this study except in compliance with applicable law. No subject-level data from the Optum Research Database or medical charts will be transferred to Lilly and/or DSI.

The claims data extracts are fully de-identified and compliant with the US Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data contained in the research 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 purposes (e.g., reporting to Centers for Medicare and Medicaid Services).

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11. Management and Reporting of Adverse Events/Adverse Reactions

Claims data extracts from the Optum Research Database include de-identified patient information and no free text data (such as that present in an EMR) will be reviewed as part of the primary claims-based analysis. Therefore, adverse event reporting is not required for the primary analysis. However, during the course of this retrospective observational research study, information pertaining to adverse reactions (ARs) for an identifiable patient may be discovered in free text data fields during patient chart review on a subset of primary study population.

11.1. Adverse Reactions

Researchers will collect all adverse reactions (ARs) when the attribution is explicitly stated in the individual patient record and is associated with any Lilly drug(s) that are under evaluation in the study via data form or electronic data entry.

Researchers will report any of the following suspected adverse reactions with attribution explicitly stated in the individual patient records to the appropriate party (for example, regulators or marketing authorization holder) as they would in normal practice as required by applicable laws, regulations, and practices:

- Any suspected adverse reactions with Lilly drug(s) not under evaluation in the study
- Any suspected adverse reaction with non-Lilly drug(s).

11.2. Serious Adverse Events

Study personnel will notify Lilly or it designee of any serious adverse reaction (SAR) with attribution explicitly stated in the individual patient medical records and arising in temporal association with the Lilly drug(s) under study in the protocol within 24 hours of awareness of the event via a sponsor-approved method. An SAR is any AR from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- or is considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events (ADRs) when, based upon appropriate medical judgement, they may jeopardize the subject.

12. 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 costs will be considered.

13. References

Footnotes are provided where relevant.

Annex 1. Quan-Charlson Comorbidity Score

Table 3. 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[31]
	Hemiplegia or paraplegia
	Renal disease
	Any malignancy, including leukemia and lymphoma
3	Moderate or severe liver disease[32]
6	Metastatic solid tumor[33]
	AIDS/HIV

[31] 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.

[32] 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.

[33] 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.

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Approver: Hsiao D. Lieu (AM\C164452)
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