PASS Information

Title	Comparison Of Clinical Outcomes, Resource Utilization, And Costs In Patients Hospitalized For ACS Managed With PCI And Receiving Prasugrel Or Ticagrelor
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Research question and objectives	Primary objective: To compare 30-day net adverse clinical events (NACE) rates in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor through 30 days, including the index hospitalization. Secondary objectives: To compare baseline demographics and patient characteristics, clinical outcomes, treatment patterns, and economic outcomes in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor.
Country of study	US
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Marketing Authorisation Holder

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

1. Table of Contents

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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
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

DX	Physician claims data asset
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
PLATO	Platelet Inhibition and Patient Outcomes
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
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.

Acute Coronary Syndrome (ACS) patients managed with percutaneous coronary intervention (PCI) (ACS-PCI)
Adult patients who had a primary or secondary ACS diagnosis at the index hospitalization and underwent PCI during the index hospitalization

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 Hospitalization
Hospitalization (e.g., pre-index hospitalization or post-index rehospitalization) for any reason

All-cause Hospitalization Costs
Costs of hospitalization for any reason

Any cardiovascular (CV) event
Any CV event (identified using primary ICD-9-CM diagnosis and/or procedure codes) of transient ischemic attack (TIA) or stroke, or rehospitalization for myocardial infarction (MI), unstable angina (UA), congestive heart failure (CHF), revascularization (PCI or coronary artery bypass graft [CABG]), or stent thrombosis.

Baseline
Baseline demographics and comorbidities will be identified by reviewing the patient's index hospitalization record as well as prior hospitalization records from as early as 1/1/2008 in the hospital charge data master files (CDM).

Bleeding
Denoted by the presence of either bleeding ICD-9 diagnosis or transfusion of whole blood (WB) or packed red blood cells (PRBC).

> <u>*Note*</u>: Severe bleeding episodes will be defined as the presence of either: Bleeding ICD-9 codes and ≥3 transfusions (between the index hospitalization date/rehospitalization date until discharge) <u>or</u> no bleeding diagnosis code and ≥4 transfusions within 2 days <u>or</u>

intracranial hemorrhage or blood transfusions followed by death for any reason within 72 hours.[1]

Bradyarrhythmia
An episode of bradyarrhythmia will be identified with a primary or secondary diagnosis code of a bradyarrthmia (see Annex 3 for specific ICD-9 codes)

Charlson Comorbidity Index
Charlson Comorbidity Index is a measure of health status, representing the number of co-morbid conditions that a patient has among a total of 22 conditions (see Annex 3 for list of comorbidities and associated ICD-9 codes). Each of these 22 conditions is assigned a weight or score of 1, 2, 3, or 6 depending on the risk of death associated with the condition. Charlson Comorbidity Index is the sum of the scores for all these conditions. The Charlson Comorbidity Index can be classified into the following categories: 0, 1, 2, 3, and over 3. The Charlson Comorbidity Index is a measure of the risk of 1-year mortality attributed to the comorbidity.[2] Primary and secondary diagnoses during the pre-index period will be used to identify the selected comorbidities and construct the Charlson Comorbidity Index. The Charlson Comorbidity Index will be calculated from the compiled comorbidity data.

Concomitant medication
A drug, other than prasugrel or ticagrelor, administered during hospitalization

CV-related Costs
If any CV event was the primary diagnosis in any hospitalization (e.g., pre-index or rehospitalization) [see definition for 'any cardiovascular event' above], all costs from that hospitalization will be attributed to that CV event and used in the calculation of CV-related costs.

Disease-related rehospitalization costs
Disease-related rehospitalization cost will be defined as hospitalization costs associated with a primary diagnosis of CV event, or primary or secondary diagnosis of bradyarrhythmia, dyspnea, or bleeding during the study period. All costs from that rehospitalization will be attributed to that diagnosis and used in the calculation of disease-related rehospitalization costs.

Dyspnea
An episode of dyspnea will be identified with a primary or secondary diagnosis code of dyspnea (see Annex 3 for specific ICD-9 codes)

Hospital length of stay
Total days from hospital admission to discharge

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[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] Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992; 45:613-9.

Hospitalization costs
As charges are provided in the database, these will be converted to costs either via available hospital-specific cost:charge ratios or citable national cost:charge ratios.

Intensive care unit/ Coronary Care Unit (ICU/CCU) length of stay
Total days in a critical care unit (e.g., ICU and/or CCU)

Index date
Index hospitalization admission date

Index hospitalization
First hospitalization during the identification period with ACS managed with PCI and in which the patient received either prasugrel or ticagrelor. First day of hospitalization (date of hospital admission) will be identified as the index date.

Major Adverse Cardiovascular Event(s) (MACE)
MACE is a composite of all-cause mortality or any CV event (as defined above).

Mortality
Identified by discharge status of "died" on the hospitalization record and/or via query of the Social Security Death Index

Myocardial infarction (MI)
An index event of myocardial infarction (MI) will be identified with a primary or secondary diagnosis of ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI). An endpoint event of MI will be identified using primary diagnosis of STEMI or NSTEMI.

Net Adverse Clinical Event(s) (NACE)
NACE is defined as the composite of MACE or severe bleeding during index hospitalization or rehospitalization for bleeding

Post-PCI length of stay
The difference between the service day of the PCI and the index discharge date (calendar day of discharge - calendar day of procedure)

Pre-index period
Period between 01/01/2008 and index hospitalization admission

Rehospitalization
An admission to any hospital within the IMS network post-discharge from an index hospitalization. Rehospitalizations will be evaluated at the patient level.

Revascularization
Rehospitalization associated with ICD-9-CM procedure codes for any target or nontarget coronary vessel revascularization (CABG or PCI)

Stent thrombosis

We assume that evidence of death or a myocardial infarction within 30-days of stenting is secondary to a probable (Academic Research Consortium [ARC] definition) stent thrombosis.[3] Additionally, as a sensitivity analysis[3], a coronary revascularization procedure post-stent placement at the index hospitalization will be added as a component of the stent thrombosis endpoint definition.

[3] Malenka DJ, Kaplan AV, Sharp SM, Wennberg JE. Postmarketing surveillance of medical devices using Medicare claims. *Health Affairs*. 2005 July/Aug;24(4):928-937.

4. Responsible Parties

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

5. Abstract

- Title: Comparison Of Clinical Outcomes, Resource Utilization, And Costs In Patients Hospitalized For ACS Managed With PCI And Receiving Prasugrel Or 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 aspirin, there is a lack of head-to-head randomized clinical trials (RCT)s or observational data that directly compares in-hospital clinical and economic outcomes between prasugrel and ticagrelor. As such, an observational retrospective database analysis will serve to fill in this important gap in the literature.

- Research Objectives: The primary study objective is to compare 30-day net adverse clinical events (NACE) rates in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor through 30 days, including the index hospitalization. Secondary objectives are to compare baseline demographics and patient characteristics, clinical outcomes, treatment patterns, and economic outcomes in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor.

- Study design: Retrospective cohort study

- Population: The primary study population will be adults with ACS managed with PCI. The following subgroups of interest for possible dissemination to "decision makers" will also be examined: Adults with ACS managed with PCI and no prior transient ischemic attack (TIA) or stroke; adults with ACS-PCI, no prior TIA or stroke, <75 years of age or ≥75 years of age with a prior MI or diabetes; adults with ACS managed with PCI with other important characteristics to be defined in the SAP. Additionally, exploratory analyses will be conducted among adults with ACS, regardless of revascularization.

- Variables: The primary dependent variable will be 30-day NACE rates. Secondary dependent variables will include clinical and economic outcomes. 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 utilization.

- Data sources: IMS Patient-Centric Data Warehouse

- Study size: Refer to section 9.4 for preliminary sample sizes in the IMS Data Warehouse. Actual study size will be determined during data lock.

- Data analysis: Descriptive analyses will be reported for all baseline variables (via appropriate measures of central tendency and inferential statistics where appropriate). Propensity score stratification will be used to adjust for potential confounding bias. Both primary and secondary categorical outcomes will be assessed as dependent variables using logistic regression models. Cohort differences in continuous outcome variables will be analyzed as dependent variables using a generalized linear model (GLM) with gamma distribution and

Poisson and/or negative binomial distribution. 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 2013 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] 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 P2Y12 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.[5,6]

Prasugrel, a P2Y12 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 who are to be managed with PCI. The TRITON-TIMI 38 trial, a randomized clinical trial (RCT) of 13,608 patients with ACS, 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 (composite primary endpoint rate was 12.1% for clopidogrel vs. 9.9% for prasugrel).[7]

More recently, ticagrelor 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]

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[4] Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. 2013;127:e6-e245.

[5] 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.

[6] 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.

[7] 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.

[8] Wallentin L., Becker R.C., Budaj A.; Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045-1057.

While the results from each RCT suggest a superior anti-thrombotic efficacy of prasugrel or ticagrelor in combination with aspirin, over clopidogrel plus aspirin, there is a lack of head-to-head RCTs or observational data that directly compares in-hospital clinical and economic outcomes between prasugrel and ticagrelor. As such, an observational retrospective database analysis will serve to fill in this important gap in the literature.

8. Research objectives

The major hypothesis of this study is that, after adjustment for baseline differences, prasugrel will be non-inferior to ticagrelor through 30 days for ACS managed with PCI in regards to net adverse clinical events (NACE). Further, when subgroups and secondary endpoints are compared, event rates with prasugrel will continue to be non-inferior to ticagrelor.

8.1. Primary Objectives

To compare 30-day NACE rates in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor through 30 days, including the index hospitalization.

NACE is defined as the composite of all-cause death, any CV event, severe bleeding during index hospitalization or rehospitalization for bleeding.

8.2. Secondary Objectives

1. To compare demographics and baseline characteristics of patients treated with prasugrel vs. ticagrelor for an ACS event managed with PCI
2. To compare bleeding (including rehospitalization for bleeding) rates in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor at 1) index hospitalization; 2) 30-days post discharge; 2) 90-days post discharge; 3) aggregate (index hospitalization through 90 days) and will be analyzed by the following criteria:
    - Any bleeding: ICD-9 bleeding codes or transfusion
        - ICD-9 Codes
        - Transfusion of whole blood (WB) or PRBC
            - ≥4 units
            - <4 units
    - Severe bleeding
        - Bleeding ICD-9 codes and ≥3 transfusions (between the index hospitalization date/rehospitalization date until discharge)
        - No bleeding diagnosis code and ≥4 transfusions within 2 days
        - Intracranial hemorrhage
        - Blood transfusions followed by death for any reason within 72 hours
3. To compare all-cause mortality rates in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor during 1) index hospitalization; 2) 30-days post discharge; 3) 90-days post discharge; 4) aggregate (index stay through 90 days)
4. To compare rates of the composite of all-cause mortality or severe bleeding in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor during 1) index hospitalization; 2) 30-days post discharge; 3) 90-days post discharge; 4) aggregate (index stay through 90 days)
5. To compare rates of the following endpoints in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor at 1) 30-days post discharge; 2) 90-days post discharge; 3) aggregate (index stay through 90 days)
    - MACE
    - NACE
    - All-cause mortality or all-cause rehospitalization

6. To compare rehospitalization rates for the following diagnoses in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor at 1) 30-days post discharge and 2) 90-days post discharge:
    - Composite of any CV Event
    - Individual components of any CV event
        - MI
        - Revascularization
        - CHF
        - UA
        - Stent thrombosis
        - TIA
        - Stroke
    - All-cause rehospitalization
7. To compare dyspnea rates in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor at 1) index hospitalization; 2) 30-days post discharge; 3) 90-days post discharge; 4) aggregate (index hospitalization through 90 days)
8. To compare bradyarrhythmia rates in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor at 1) index hospitalization; 2) 30-days post discharge; 3) 90-days post discharge; 4) aggregate (index hospitalization through 90 days)
9. To compare the following economic outcomes in ACS patients managed with PCI and treated with prasugrel vs. ticagrelor
    - Resource utilization during the index hospitalization
        - ICU/CCU length of stay (LOS)
        - Post-PCI LOS (day after PCI is day 1)
        - Hospital overall LOS
        - General laboratory and diagnostic tests
    - Hospitalization costs (CV-related and all-cause) at 1) index hospitalization stay; 2) 30-days post-discharge; 3) 90-days post-discharge 4) aggregate (index hospitalization through 90 days)
        - Total (medical and pharmacy)
            - Medical
                - Accommodations (e.g., general floor, ER, OR, ICU, etc.)
                - Medical surgical supplies
                - Lab tests
                - Diagnostic procedures
            - Pharmacy
                - Treatments (e.g., drugs, chemotherapy, radiation)
        - Rehospitalization for
            - Composite of any CV Event
            - Individual components of any CV event
                - MI
                - Revascularization
                - CHF
                - UA

        - Stent thrombosis
        - TIA
        - Stroke
    - Dyspnea
    - Bradyarrhythmia
    - Bleeding
    - All-cause

10. To compare the following in-hospital treatment patterns between ACS patients managed with PCI and using prasugrel vs. ticagrelor at 1) index hospitalization stay; 2) 30-days post-discharge; 3) 90-days post-discharge; and, 4) aggregate (index hospitalization through 90 days):
    - Concomitant use of selected medications (as listed in section 9.2)
    - Procedures of Interest
        - PCI procedure
            - Number of vessels
            - Number of stents
                - Drug-eluting stent (DES) implantation
                - Bare metal stent (BMS) implantation
                - No stent implantation
        - CABG surgery

8.3. Exploratory Objective

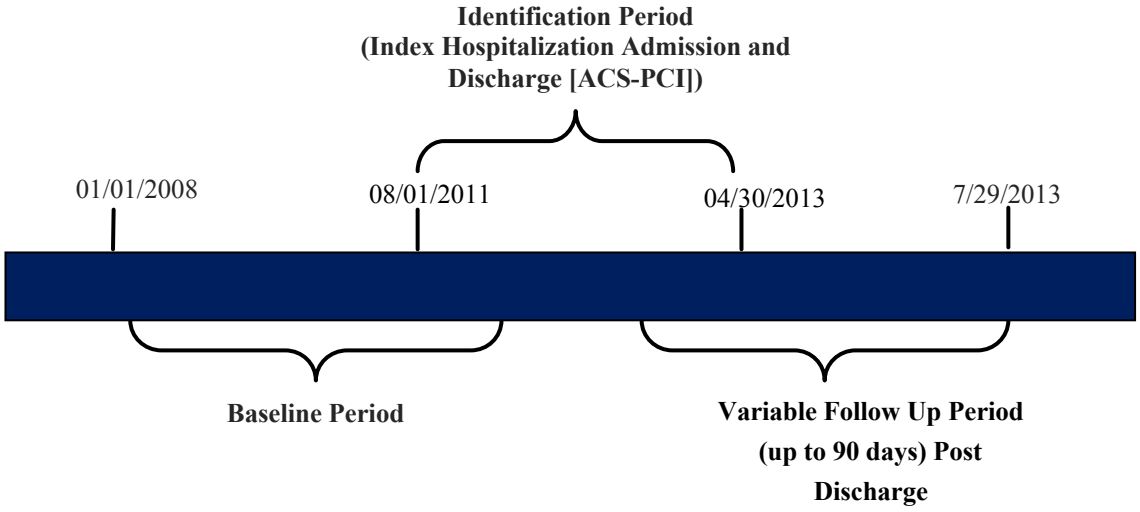
- To compare demographics and baseline characteristics of patients treated with prasugrel vs. ticagrelor during index hospitalization for an ACS event, regardless of treatment pathway.

9. Research methods

9.1. Study design

9.1.1.1. *Timeframe for the primary and secondary objectives*

Figure 1.



9.1.1.2. *Inclusion criteria*

Primary study population: ACS-PCI population

Patients meeting the following inclusion criteria (during the timeframe specified) will be selected to study the primary and secondary objectives:

- Index hospitalization admission and discharge between August 1, 2011 and April 30, 2013 with a primary or secondary diagnosis of ACS (index ACS hospitalization) managed with PCI (see Annex 3 for codes).
- At least one hospital claim for prasugrel or ticagrelor during index ACS-PCI hospitalization.
- Aged ≥18 years as of index ACS-PCI hospitalization admission

Exploratory study population: Overall ACS population

- Index hospitalization admission and discharge between August 1, 2011 and April 30, 2013 with a primary or secondary diagnosis of ACS (index ACS hospitalization) (see Annex 3 for codes).
- At least one hospital claim for prasugrel or ticagrelor during index ACS hospitalization.
- Aged ≥18 years as of index ACS hospitalization admission

9.1.1.3. *Exclusion Criteria*

- Patients with hospital claims for both ticagrelor and prasugrel during the same index hospitalization

9.1.1.4. *Subgroups of interest*

ACS-PCI subgroups of interest for possible dissemination to "decision makers" will be as follows:

- Adults with ACS managed with PCI and no prior TIA or stroke
- Adults with ACS-PCI, no prior TIA or stroke, <75 years of age, or ≥75 years of age with prior MI or diabetes
- Adults with ACS managed with PCI with other important characteristics to be defined in the SAP

Not all analyses will be performed in each subgroup. Subgroup specific analyses will be specified in the SAP.

No subgroups of the overall ACS (regardless of revascularization) population will be examined.

9.2. Variables

Baseline Demographic and Clinical Characteristics

- Prior ACS diagnosis (n, %) (look at all hospitalizations from 1/2008 forward, up to but not including index hospitalization)
  - MI
  - UA
- Current ACS diagnosis (n, %) (index hospitalization)
  - STEMI
  - NSTEMI
  - UA
- Age in years (mean and standard deviation [SD], median) (index hospitalization)
- Age (n, %) (index hospitalization)
  - 18-44 years
  - 45-54 years
  - 55-64 years
  - 65-74 years
  - ≥75 years
- Hospital type (n, %) (index hospitalization)
  - Geographic region
  - Number of beds
  - Urban/rural
  - Teaching/non-teaching

- Gender (n, %) (index hospitalization)
- Primary payer type (n, %) (index hospitalization)
- Comorbidities (n, %) (look at all hospitalizations from 1/2008 forward, including index hospitalization)
  - Anemia
  - Arterial embolism
  - Asthma
  - Atrial fibrillation
  - Cardiac dysrhythmia
  - Cardiomyopathy
  - Cerebrovascular disease
  - COPD
  - Deep venous thrombosis
  - Diabetes
  - Dyslipidemia
  - Dyspnea
  - CHF
  - CKD
  - Hemorrhagic stroke
  - Hemorrhagic tendencies of blood dyscrasia
  - History of bleeding
  - Hypertension
  - Hypotension
  - Ischemic Heart Disease, other than ACS (MI or UA)
  - Ischemic stroke or TIA
  - Liver disease
  - Obesity
  - Osteoarthritis
  - Peripheral vascular disease
  - Phlebitis
  - Pulmonary embolism
  - Renal Insufficiency
  - Rheumatoid Arthritis
  - Sepsis
  - Thyrotoxicosis
- Charlson Comorbidity Index (mean and SD, median) (index hospitalization)
- Prior CABG (n, %) (look at all hospitalizations from 1/2008 forward, up to, but not including index hospitalization
- Prior PCI (n, %) (look at all hospitalizations from 1/2008 forward, up to, but not including index hospitalization)

Baseline Treatment Utilization

- ADP receptor inhibitors

    - Clopidogrel
    - Prasugrel
    - Ticagrelor
    - Ticlopidine
  - Phosphodiesterase inhibitors
    - Cilostazol
  - HMG CoA reductase inhibitors (statins)
  - Proton Pump Inhibitors (PPIs)
  - Diabetes medications
    - Parenteral agents
    - Oral agents
  - Antihypertensive agents
    - ACE inhibitors
    - Angiotensin II receptor blocker (ARB)
    - Beta blockers
    - Calcium channel blockers
    - Direct renin inhibitors
    - Loop diuretic
    - Potassium sparing diuretics
    - Thiazide diuretics
    - Other anti-hypertensives
  - One year pre-index resource utilization and costs (hospital CDM only)
    - Costs to be reported as 'any CV event-related', 'disease-related', 'all-cause' (mean, SD, median)
    - Utilization to be reported as mean (SD) and median number of hospitalizations

Clinical Outcomes

- Any bleeding
  - By ICD-9 codes or transfusion
    - By ICD-9 Codes
    - By Transfusion of WB or PRBC
      - ≥4 units
      - <4 units
- Severe bleeding
  - Bleeding ICD-9 codes and ≥3 transfusions (between the index hospitalization date/rehospitalization date until discharge)
  - No bleeding diagnosis code and ≥4 transfusions within 2 days
  - Intracranial hemorrhage
  - Blood transfusions followed by death for any reason within 72 hours
- All-cause mortality
- Dyspnea
- Bradyarrhythmia
- Composite

- All-cause mortality or severe bleeding
- MACE (Any CV event)
- NACE
- All-cause mortality or all-cause rehospitalization
- Individual components of any CV event
  - MI
  - Revascularization
  - CHF
  - UA
  - Stent thrombosis
  - TIA
  - Stroke
- All-cause rehospitalization

In-hospital Economic Outcomes

- Healthcare resource utilization during the index hospitalization
  - ICU/CCU LOS
  - Post-PCI LOS (day after PCI is day 1)
  - Overall LOS
- Laboratory and diagnostic tests
  - Coronary angiography
  - Cardiac magnetic resonance imaging (MRI)
  - CT angiography
  - Cardiac stress test
  - Complete Blood Count (CBC) or Hemoglobin
  - Serum creatinine
  - Electrocardiogram (ECG)
  - Chest x-ray (CXR)
  - Pulmonary function tests (PFT)
- Hospitalization costs (CV-related and All-cause)
  - Total (medical and pharmacy)
    - Medical
      - Accommodations (e.g., general floor, ER, OR, ICU, etc.)
      - Medical surgical supplies
      - Lab tests
      - Diagnostic procedures
    - Pharmacy
      - Treatments (e.g., drugs, chemotherapy, radiation)
  - Rehospitalization for
    - Composite of any CV Event and its components
      - MI
      - Revascularization
      - CHF

        - UA
        - Stent thrombosis
        - TIA
        - Stroke
    - Dyspnea
    - Bradyarrhythmia
    - Bleeding
    - All-cause

In-hospital Treatment Patterns

- Concomitant use of the following selected medications
    - Digoxin
    - Statins
    - Calcium channel blockers
    - ACEi/ARB
    - Beta blockers
    - Fibrinolytic therapy*
    - Adenosine reuptake inhibitors*
        - Dipyridamole
    - Glycoprotein IIb/IIIa inhibitors*
        - Abciximab
        - Eptifibatide
        - Tirofiban
    - Anticoagulant (separate into oral/IV formulations)*
        - Unfractionated heparin
        - Low molecular weight heparin
        - Pentasaccharide (fondaparinux)
    - Direct thrombin inhibitor*
        - Bivalirudin
    - Oral anticoagulant or antithrombin*
        - Rivaroxaban
        - Dabigatran
        - Apixaban
        - Coumadin

*Use of these medications ≤ 7 days prior to study index date (index hospitalization admission) through index hospitalization discharge will be considered as in-hospital treatment utilization.

- CYP3A4 inducers and inhibitors
    - CYP3A inhibitors
        - Ketoconazole
        - Itraconazole
        - Voriconazole
        - Telithromycin

        - Clarithromycin
        - Nefazodone
        - Ritonavir
        - Saquinavir
        - Nelfinavir
        - Indinavir
        - Atazanavir
    - CYP3A substrates with narrow therapeutic indices
        - Cyclosporine
        - Quinidine
    - CYP3A inducers
        - Rifampin/rifampicin
        - Phenytoin
        - Carbamazepine
        - Dexamethasone
        - Phenobarbital
- Diagnoses or procedures during index hospitalization
    - PCI procedure
        - Number of stents
            - DES implantation
            - BMS implantation
            - No stent implantation
        - Number of vessels
    - CABG
    - Left ventricular assist device
    - Defibrillator implantation
    - Pacemaker implantation
- Treatment patterns during any rehospitalization through 90-days post-discharge
    - Concomitant use of selected medications
    - PCI procedure during rehospitalization (if performed)
        - Number of stents
            - DES implantation
            - BMS implantation
            - No stent implantation
        - Number of vessels
    - CABG
    - Left ventricular assist device
    - Defibrillator implantation
    - Pacemaker implantation

9.3. Data sources

The IMS Patient-Centric Data Warehouse will be used for analysis. The warehouse, acquired by IMS in 2011, extracts de-identified data from all healthcare channels in the US, including hospitals, providers and pharmacies. Data sources include medical claims, pharmacy claims and hospital charge master records. Patient identifiers in all data sources are pre-processed using a proprietary, one-way encryption algorithm, so that patients may be linked across sources where patients overlap among data contributors.

Professional Fee Claims
Approximately 1 billion professional fee claims per year are submitted, representing over 870,000 practitioners per month. Records are available from September 1999, with approximately 95% of claims available for analyses within 3 weeks of the service date. Over time, there is representation from approximately 236 physician specialties (e.g., American Medical Association (AMA) classifications such as Family Medicine, Pediatrician, Radiologist, Urologist, etc.) as well as representation of non-physician practitioners (e.g., Nurse Practitioners and Physicians Assistants). The data include patient demographics, diagnoses, procedures, and in-office administered drugs.

Prescription Claims
Through agreements with a variety of data contributors, the warehouse includes more than 1.6 billion retail or mail-order prescription claims, representing dispensed prescriptions for approximately 55% of all pharmacies in the US. Available from April 2001, approximately 95% of claims are available for analyses within 12 days of being dispensed. National Council for Prescription Drug Programs (NCPDP) claims include those reimbursed by cash, Medicare, Medicaid and other third party transactions.

Hospital Charge Master
The warehouse includes records from hospital charge data master (CDM) files, the service order records drawn from hospital operational files and other reference sources. The warehouse includes records from over 650 hospitals, covering 7 million annual in-patient stays and 60 million annual outpatient visits. Data elements include all in-patient and outpatient encounters within a facility, linked to individual departments, with detailed drug, procedure, diagnosis, and applied charge data for the entire stay. Patient demographics and admission/discharge characteristics are also available for each facility stay. Data are available from 2001, with a data lag time of 6 weeks following the end of each calendar month.

Note: To meet the objectives of our study, the warehouse will be linked with the Social Security Death Index (SSDI). There is a data lag time of 12 weeks following the end of each calendar month.

9.4. Study size

Table 1 provides preliminary sample sizes available in the IMS Data Warehouse for the following study cohorts: 1) patients with ACS, 2) patients with ACS managed with PCI during the same hospitalization (primary study cohort), and 3) patients with ACS managed with PCI during the same hospitalization and with no prior TIA or stroke.

Table 1. Number of Patients Available for Analysis as of Cut-off Date of April 30, 2013

Step 1	Subset of Step	Criteria	Count
1	N/A	Count of distinct ACS-related inpatient stays with presence of prasugrel (Date of hospital **admission and discharge** within the study period [Time period of 8/1/11 – 4/30/13, CDM data])	21,978
2	N/A	Count of distinct ACS-related inpatient stays with presence of ticagrelor (Date of hospital **admission and discharge** within the study period [Time period of 8/1/11 – 4/30/13, CDM data])	5,205
3	1	Count of distinct patients from step 1 that have PCI in the hospitalization in the CDM data	19,153
4	2	Count of distinct patients from step 2 that have PCI in the hospitalization in the CDM data	4,247
5	3	Count of distinct patients from step 3 with no prior TIA or stroke since January 2008 within the CDM data	18,316
6	4	Count of distinct patients from step 4 with no prior TIA or stroke since January 2008 within the CDM data	4,019
7	5	Count of patients from step 5 after removing patients (N=1,063) that also have ticagrelor during the hospital admission	17,253
8	6	Count of patients from step 6 after removing patients (N=454) that also have prasugrel during the hospital admission	3,565

Codes are listed in the SAP.

9.4.1. Sample Size

For the ACS-PCI population with no prior TIA or stroke, and received prasugrel or ticagrelor (but not both) during the index hospitalization (Steps 7 and 8 in Table 1), the above sample sizes will provide over 80% power to declare non-inferiority assuming a base rate of 6.0% for NACE through 30 days including index hospitalization and a noninferiority margin in which the upper limit of the 95% CI for the point estimate should not exceed 1.2, using a one-sided alpha level of 0.05 (95% one-sided confidence interval).

9.5. Data management

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

9.6. 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[9] 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.

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). Details will be provided in the SAP. 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, max and interquartile range (IQR) for continuous variables. Differences between cohort will be assessed using Chi-square test for

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[9] 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.

categorical variables and, t-test and ANOVA for continuous variables. Exact tests, bootstrapping and/or nonparametric tests will be used as appropriate.

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.

9.6.4. Propensity Score Creation and Deciles

Propensity score stratification will be used to adjust potential confounding bias.[10,11] The adjusted (propensity score stratified) analyses will be considered the primary analysis. Propensity score for each patient will be defined as the probability of being in the prasugrel cohort and estimated using logistic regression.

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, baseline treatment utilization measures, and in-hospital treatment patterns (listed in section 9.2 and Annex 3) 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.[12,13,14,15,16,17,18]

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

[11] 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.

[12] 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.

[13] 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.

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

[15] 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.

[16] 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.

[17] 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.

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 is 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.

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, and side-by-side boxplots or histograms).[19] As a rule of thumb, standardized differences greater than 0.10 indicate imbalance that may require further investigation.[20] The propensity model will be finalized prior to initiating analysis of the outcome measure.

9.6.5. Propensity- Adjusted Analyses

Categorical (binary) outcome variables associated with both the primary and secondary objectives, including separate endpoints for bleeding, mortality, and dyspnea rates, will be assessed as dependent variables using logistic regression. Treatment cohort (prasugrel or ticagrelor), propensity score strata (as a categorical variable), and the cohort- by- propensity score strata interaction term will be included as independent variables in the model.

Cohort differences will be summarized using both the estimated odds ratios and risk differences from this model. The estimated risk differences from the final model will be computed by

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[18] 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.

[19] 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

[20] 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

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.

Cohort differences in continuous outcome variables will be analyzed as dependent variables using GLMs to model costs (with gamma specification) as well as resource use outcomes and treatment patterns (with Poisson and/or negative binomial specifications). Treatment cohort (prasugrel or ticagrelor), propensity score strata, and the cohort-by-propensity score strata interaction term will be included as independent variables in the model. Least squares means and 95% confidence intervals will be estimated on the difference in means. Alternative and more appropriate models may be employed after assessment of the observed distribution of continuous dependent variables and prior to any outcomes analyses.

9.6.6. Sensitivity Analyses

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), a sensitivity analysis will be conducted using the rule-out method.[21]

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.

To assess the robustness of the results to modeling assumptions, method selection, and other statistical assumptions, alternative methods will 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.[24] Therefore, CLT-based methods (ANCOVA or traditional OLS models) will be used as a sensitivity analysis of costs 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 will 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 will be assessed by examining any exclusion of patients during the selection process.

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[21] Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. pharmacoepidemiology and drug safety 2006; 15: 291–303.
[22] 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

Sensitivity analyses will also be conducted using the primary methods/models but:

- Excluding patients selected during the first 3 months of the patient identification window (i.e., using an identification 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;
- Using a 12-month pre-index hospitalization data stability period
    - A 12-month pre-index hospitalization data stability criteria (i.e., all study patients will be required to have at least 12-month continuous outpatient data stability [determined via linkage to at least one Dx claim, through Dx data asset] prior to study index date) will be applied for sensitivity analysis.

Specific details on sensitivity analyses will be stated in the SAP prior to conducting the analyses.

9.7. Quality control

IMS undertakes an extensive data validation and correction process that includes quality assurance checks. Level 1 involves data acquisition certification by individual data contributors. Level 2 involves extract/transform/load certification. Level 3 addresses warehouse load certification. Level 4 includes an independent external actuarial review.

9.8. Limitations of the research methods

Limitations of this study include those inherent in any retrospective cohort studies using administrative claims and hospital charge master data.

- 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.
- Patients observed in the database may receive care at another site (e.g., out-of-network or outside of data capture) resulting in loss of information. Along those lines, rehospitalization to a non-IMS charge master hospital are not captured and are not likely a source of bias.
- 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.
- 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 from this data source.
- Data entry errors may exist at the site of care.

9.9. Other aspects

- Bleeding (based on ICD-9 codes or transfusion during index hospitalization and/or rehospitalization) will be assessed as a safety endpoint in this study. Of note, the definition of bleeding in this study is different from those used in RCTs (e.g., TIMI major and minor); hence, a direct comparison of safety results (e.g., bleeding) from this study and the TRITON-TIMI 38 trial should not be made.
- Not all patients found in the hospital (CDM) dataset are linkable to outpatient (Dx dataset) data in the pre-index period; hence, a 12-month continuous outpatient data stability (via Dx linkage) criteria in the pre-index period will not be applied for the primary analysis. Instead, baseline characteristics will be determined by reviewing the patient's index hospitalization record as well as prior hospitalization records from as early as 1/1/2008 in the CDM with no linkage to outpatient data. This limitation is inherent in payer hospital database analyses.[15,19,20] A sensitivity analysis using a subset with at least 12-month continuous outpatient data stability (via Dx linkage) in the pre-index hospitalization period will be conducted (see Section 9.6.6).

10. 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 IMS Patient-Centric Data Warehouse 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 (e.g., 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 IMS Patient-Centric Data Warehouse will not be transferred to Lilly and/or DSI.

11. Management and reporting of adverse events/adverse reactions

Not applicable. Data extract includes de-identified patient information and no free text data (such as that present in an EMR) will be reviewed as part of this project. Therefore, adverse event reporting is not required.

12. Plans for disseminating and communicating study results

The list below identifies the dissemination plan for this study;

Q4/2013	Internal communication of study findings
Q1/2014	External disclosure: abstract, presentation (poster or oral), manuscipt
Q2/2014	Response to customer questions
Q2/2014	FDAMA 114 promotional piece

13. References

Provided as footnotes where relevant.

Annex 1. List of stand-alone documents

Not applicable.

Annex 2. ENCePP Checklist for study protocols

Not applicable.

Annex 3. Additional Information

All diagnoses and procedure codes will be listed in the statistical analysis plan (SAP).

List of Independent Variables for the Propensity Model

Age	years (mean and standard deviation [SD], median)
	n, % 18-44 years 45-54 years 55-64 years 65-74 years ≥75 years
Hospital	n, % Geographic region Number of beds Urban/rural Teaching/non-teaching
Gender	n, % Male Female
Primary payer type	n, %
ACS-diagnosis	STEMI NSTEMI UA
Comorbidities	n, % Anemia Arterial embolism Asthma Atrial fibrillation Cardiac dysrhythmia

	Cardiomyopathy Cerebrovascular disease COPD Deep venous thrombosis Diabetes Dyslipidemia Dyspnea CHF Hemorrhagic stroke Hemorrhagic tendencies of blood dyscrasia History of bleeding Hypertension Hypotension Ischemic Heart Disease, other than ACS (MI or UA) Ischemic stroke or TIA Liver disease Obesity Osteoarthritis Peripheral vascular disease Phlebitis Pulmonary embolism Renal Insufficiency Rheumatoid Arthritis Sepsis Thyrotoxicosis
Charlson Comorbidity Index	mean and SD, median
Prior CABG	n, %

Prior PCI	n, %
Index Hospitalization, PCI: Number of vessels	mean and SD, median
Index Hospitalization, PCI: Number of stents	mean and SD, median
Index Hospitalization, PCI: Drug-eluting stent implantation	n, %
Index Hospitalization, PCI: Bare-metal stent implantation	n, %
Index Hospitalization: Left ventricular assist device	n, %
Index Hospitalization: Defibrillator implantation	n, %
Index Hospitalization: Pacemaker implantation	n, %
Other Drug Therapy	
Digoxin	n, %
Fibrinolytic therapy	n, %
ADP receptor inhibitors	n, % Clopidogrel Prasugrel Ticagrelor Ticlopidine
Phosphodiesterase inhibitors	n, % Cilostazol

Adenosine reuptake inhibitors	n,% Dipyridamole
Glycoprotein IIb/IIIa inhibitors	n, % Abciximab Eptifibatide Tirofiban
Anticoagulant (separate into oral/IV formulations)	n, % Unfractionated heparin Low molecular weight heparin Pentasaccharide (fondaparinux)
Direct thrombin inhibitor	n, % Bivalirudin
Other anticoagulant or antithrombin	n, % Rivaroxaban Dabigatran Apixaban Coumadin
HMG CoA reductase inhibitors (statins)	n, %
Proton Pump Inhibitors (PPIs)	n, %
Diabetes medications	n, % Insulin Oral agents

Antihypertensive agents	n, % ACE inhibitors Angiotensin II receptor blocker (ARB) Beta blockers Calcium channel blockers Direct renin inhibitors Loop diuretic Potassium sparing diuretics Thiazide diuretics Other anti-hypertensives
Pre-index resource utilization and costs (CV-related and All-cause)	Mean (SD) and median number of hospitalizations
	Mean (SD) and median prior hospitalization costs

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