ARTEMIS

Affordability and Real-world Antiplatelet Treatment Effectiveness After Myocardial Infarction Study

Statistical Analysis Plan

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[Confidential]

ARTEMIS

Affordability and Real-world Antiplatelet Treatment Effectiveness After Myocardial Infarction Study

Study Statistician [redacted]

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1. Overview

The purpose of the statistical analysis plan is to describe the key components of the Affordability and Real-world Antiplatelet Treatment Effectiveness After Myocardial Infarction Study final data analysis. This plan is a supplement to the materials provided in the ARTEMIS protocol (version date: March 12, 2015).

ARTEMIS is a prospective cluster-randomized clinical trial that will evaluate whether patient copayment reduction significantly influences antiplatelet selection and long-term adherence. This study will also examine patient outcomes and the overall cost of care after AMI. After IRB approval, sites will be randomized to either the intervention or the control. Randomization will be stratified by annual site AMI volume and proportion of ticagrelor use using medians across potential sites as cut-offs for identifying high vs. low categories. Approximately 11,000 patients with STEMI or NSTEMI will be enrolled at approximately 300 hospitals.

1.1 Primary Objectives

The co-primary objectives of ARTEMIS are the following:

To determine if patient copayment reduction leads to higher long-term persistence of any $P2Y_{12}$ receptor inhibitor at one year after discharge.

To determine if patient copayment reduction leads to lower risk of MACE (composite of death, AMI, and stroke) at one year after discharge.

1.2 Secondary Objectives

To evaluate whether reducing patient copayments affects selection of $P2Y_{12}$ receptor inhibitor medication at discharge.

To assess the impact of copayment reduction on the total cost of health care for patients after AMI.

1.3 Site and Patient Inclusion Criteria

Study Site Selection Criteria
Hospitals are eligible to be included in the study if they meet the following criteria:

[1] Treat at least 50 STEMI or NSTEMI patients annually
[2] Have clopidogrel and ticagrelor available for clinical use on their hospital formulary

Study Patient Selection Criteria
Patients are eligible to be included in the study if they meet all of the following criteria:

[1] Are ≥18 years of age

[2] Have been diagnosed with STEMI or NSTEMI during the index hospitalization
- STEMI is defined as symptoms of cardiac ischemia (e.g., chest pain) associated with either a new left bundle branch block or ST-segment elevation of ≥1 mm in at least two contiguous leads on the electrocardiogram (ECG). If no reperfusion treatment is pursued, patients must be treated with primary PCI or fibrinolytic therapy, or have at least one troponin I, troponin T, or creatine kinase-MB value greater than the institutional upper limit of normal.
- NSTEMI is defined as symptoms of cardiac ischemia associated with a rise and fall in biomarkers indicating myocardial necrosis. At least one troponin I, troponin T, or creatine kinase-MB value must be greater than the institutional upper limit of normal.

[3] Are treated with a $P2Y_{12}$ receptor inhibitor at the time of enrollment
[4] Have United States-based health insurance coverage with prescription drug benefit
[5] Have been fully informed and are able to provide written consent for longitudinal follow-up

Patients are excluded if they meet any of the following criteria:
[1] Have a history of prior intracranial hemorrhage
[2] Have any contraindications to $P2Y_{12}$ receptor inhibitor therapy at discharge
[3] Involvement in another research study that specifies the type and duration of $P2Y_{12}$ receptor inhibitor use within the next 12 months
[4] Have a life expectancy of less than one year
[5] Have plans to move outside the United States in the next year

1.4 Sample Size Justification

The proposed sample size has been determined to provide adequate statistical power for the co-primary study objectives related to the copayment reduction intervention. The co-primary objective determines whether patient copayment reduction leads to greater persistence to $P2Y_{12}$ receptor inhibitor therapy at one year after hospital discharge. The hypothesis underlying this objective is that reducing patient copayment in a contemporary population of AMI patients will result in a significant increase in persistence to $P2Y_{12}$ receptor inhibitor therapy at one year, when compared with usual care. An increase of 4% in the persistence to $P2Y_{12}$ receptor inhibitor therapy would be considered a clinically important difference[1]. To achieve this objective with a patient-level randomization design, a sample size of 5392 patients would provide greater than 90% power with a two-sided Type I error rate of 0.05. A sample size of 4622 patients would provide greater than 85% power under the same assumptions. These power calculations are based on the assumption that the expected one-year persistence rate in the control group is 70%[1]. These calculations are based on the two group continuity corrected chi-square test statistic and assume that all observations are independently distributed. However, the sample size needs to be adjusted due to the cluster randomized design. We have applied the method described by Eldridge et al. [2] which accounts for the coefficient of variation (CV) of cluster

size and the intra-cluster correlation (ICC). Based on prior multicenter studies, we anticipate an ICC for this endpoint of approximately 0.025. Assuming a total of 300 sites randomized (1:1) with an average sample size of 36.67 patients per site and a CV of 0.65 would yield a design effect of approximately 2.28. The CV of 0.65 has been suggested by others and can be guided by providing minimum and maximum enrollment at the site level [2]. Therefore, a total sample size of 11,000 patients enrolled at 300 sites would result in an effective sample size of 4827 and be sufficient to provide between 85% and 90% power to detect an absolute 4% difference between treatment groups in the cluster randomized design.

For the one-year MACE endpoint, the underlying hypothesis is that patient copayment reduction leads to a reduction in MACE risk; this is partially due to the selection of a more potent antiplatelet agent that has been shown to reduce MACE risk in randomized clinical trials, and partially due to greater persistence of an evidence-based secondary prevention medication. For this endpoint, we have assumed a control group event rate of 12%. A clinically meaningful event reduction of 18% would yield a one-year event rate of 9.84% [3]. To achieve 80% power with a patient-level randomization, a 1:1 allocation ratio, and a two-sided Type I error rate of 0.05 would require a total of 6728 patients. Under the same assumptions, a total sample size of 7670 would provide 85% power. These sample size estimates are based on the continuity corrected chi-square test. Since the unit of randomization will be the site rather than the individual, we again need to consider the correlation of response within site and the CV on the number of patients enrolled per site. Prior multicenter studies have suggested an ICC of approximately 0.01 for the MACE endpoint [2]. A total sample size of 11,000 patients enrolled at 300 sites, assuming an ICC of 0.01 and a CV of 0.65, would yield an effective sample size of 7278 patients (Table). Therefore, the total sample size of 11,000 patients enrolled at 300 sites would be expected to provide between 80% and 85% power to detect an 18% relative reduction in MACE (12.0% vs. 9.84%).

Table: Required Sample Size for the MACE Endpoint

Sites	Total Sample Size	Average # of Patients per Site	ICC	CV	Effective Sample Size
250	10000	40	0.010	0.65	6414
250	11000	44	0.010	0.65	6808
250	12000	48	0.010	0.65	7174
250	13000	52	0.010	0.65	7516
250	14000	56	0.010	0.65	7836
250	15000	60	0.010	0.65	8137
250	16000	64	0.010	0.65	8420
250	17000	68	0.010	0.65	8686
250	18000	72	0.010	0.65	8936
300	10000	33.33	0.010	0.65	6830
300	**11000**	**36.67**	**0.010**	**0.65**	**7278**
300	12000	40	0.010	0.65	7698
300	13000	43.33	0.010	0.65	8092
300	14000	46.67	0.010	0.65	8466
300	15000	50	0.010	0.65	8818
300	16000	53.33	0.010	0.65	9150

300	17000	56.67	0.010	0.65	9465
300	18000	60	0.010	0.65	9764

Patient-reported persistence to antiplatelet therapy will be validated using pharmacy records that will be collected on a subset of the overall study population. The assumed standard deviation of 0.25 (for the proportion of days covered) is based on a recent randomized clinical trial to assess an intervention designed to improve adherence [4]. Assuming 1:1 randomization and a two-sided Type I error rate of 0.05, a sample size calculation based on the two-sample t-test suggests that a total sample size of 1644 patients will yield 90% and a total sample size of 2034 will yield 95% power. A random sample of 2400 patients from the 300 sites randomized with a CV of 0.25 and an ICC of 0.025 would yield a design effect of approximately 1.26. The resulting effective sample size of 2021 patients would yield approximately 95% power to detect a difference of 4% between the patient copayment reduction intervention and control groups. The target sample size of 2500 patients with pharmacy records allows for 4% missing data due to records that are not available.

2. General Considerations for Data Analysis

We will include a detailed flow diagram showing the number of participants' eligible, number of subjects randomized to Copayment Invention and Usual Care arms, numbers of subjects lost to follow-up or excluded from analyses, and the number of subjects analyzed for the key study endpoints. Additionally, we will describe the number of clinical sites in Copayment Intervention and Usual Care arms including the mean (median, range) for key study elements by site. Key elements will include the following items: descriptions of participants, interventions, objectives, outcomes, and sample size justification; and details about the randomization procedure, factors used to stratify randomization, (lack of) blinding, statistical methods, participant flow, dates of recruitment, baseline data by individuals and by cluster, numbers analyzed, outcomes and estimation, adverse events, and a discussion. These elements are based on the CONSORT statement for cluster randomized studies [5].

After Steering Committee consensus, the randomization scheme was changed from 1:1 to 2:1 Usual Care vs. Intervention effective November 16, 2015. Randomization schema was added below as a covariate for adjustment.

All analyses will be conducted using SAS version 9.4 or higher software. All tests will be two-sided and a p-value of <0.05 will be considered statistically significant.

2.1 Analysis Datasets and Baseline Comparisons

Data from all enrolled patients, regardless of whether or not they completed all protocol follow-up requirements, will be included for analysis. Baseline comparisons of patient characteristics and randomization stratification variables between intervention and control arms groups will be summarized as the mean; standard deviation; median; and 25th, 75th percentiles for continuous variables; and as counts and percentages for categorical variables. We will present baseline

characteristics and randomization stratification variables at both the patient and cluster levels. Cluster level summary data will be presented as means (standard deviations). All study objectives will be analyzed using intention-to-treat analyses.

2.2 Analysis Populations

The study population for primary and secondary analyses in ARTEMIS will start with all enrolled patients who survived the index MI hospitalization and did not withdraw from the study before hospital discharge. Since the intervention arm voucher provides copayment assistance for a generic (clopidogrel) or a brand (ticagrelor) $P2Y_{12}$ receptor inhibitor, we will conduct the primary endpoint analyses first among patients discharged on either clopidogrel or ticagrelor, and then repeat the analysis among all patients regardless of discharge $P2Y_{12}$ receptor inhibitor type.

2.3 Accounting for Hospital Clustering: Marginal vs. Conditional Modelling Approaches for Binary Endpoints

There are two general approaches that account for within hospital correlation in a statistical model; they are 1) marginal or population-averaged model and 2) conditional or subject-specific model. These two approaches differ in interpretation of model estimates and the way that correlation of measurements are incorporated in the model. For example, under the marginal model, the exponentiated treatment coefficient represents the odds of an average patient in the treatment group to be persistent compared to an average patient in the control group. Under the conditional random-effects model, the exponentiated treatment coefficient represents the odds of persistence for a treated person compared to the same person if they were not treated. As stated in the protocol we will use population averaged methods as our primary approach to account for hospital clustering.

2.4 Missing Data

Operational efforts will be made to minimize missing data at baseline and during follow-up. During the enrollment phase, baseline data will be reviewed on a monthly basis and sites will be notified regarding any data quality concerns. Study personnel will confirm that missing data cannot be obtained. Follow-up data will be regularly reviewed after 50% of patients reach 3 months post-discharge.

We will impute socioeconomic variables, lab values, and weight to age, gender, and race specific modes for categorical variables and medians for continuous variables. Medical history, home medications, admission features, and in-hospital events will be imputed to the mode.

3 Primary Endpoints

3.1 Non-persistence with antiplatelet therapy at 1 year

The co-primary endpoint of long-term non-persistence will be assessed using patient-reported medication non-persistence. Permanent and temporary discontinuation of a $P2Y_{12}$ receptor inhibitor will be queried at each follow-up interview. For patients with missing patient-reported medication information, pharmacy fill data will be used to ascertain persistence. Patients who have continued $P2Y_{12}$ receptor inhibitor use at one year from discharge with less than 30

continuous days of interruption will be considered persistent. We will use the last observation carried forward (LOCF) method for patients who died before one year or had missing 1 year $P2Y_{12}$ status.

The co-primary objective determines whether patient copayment reduction leads to higher long-term persistence with antiplatelet therapy at one year. The study endpoint for this objective is the proportion of patients at one year who had an interruption ≥30 days of $P2Y_{12}$ receptor inhibitor. The primary analysis will be a logistic regression model with parameters estimated using generalized estimating equations (GEE) to account for within hospital clustering and adjustment for selected patient characteristics (Section 8.3.1) which includes a propensity score for intervention (Section 8.3.2). The propensity score will be estimated using a logistic regression model for intervention group. Categorical variables will be included as sets of indicator variables. Continuous variables will be included assuming a simple linear relationship. Balance of covariates between intervention and usual care arms will be assessed using standardized differences as recommended by Austin [6]. We will assess functional form and possible transformations of the propensity score to be included in the outcome model. Cluster heterogeneity will be quantified using ICCs calculated from unadjusted and adjusted models. We will calculate the ICCs across all hospitals and also by treatment group.

After Steering Committee consensus, the randomization scheme was changed from 1:1 to 2:1 Usual Care vs. Intervention effective November 16, 2015. Randomization schema was added as a covariate for adjustment as shown in Section 8.3.1 and to the propensity model as shown in Section 8.3.2.

3.2 MACE

The primary study objective evaluates whether patient copayment reduction leads to lower risk of MACE at one year. MACE is defined as the composite of all-cause death, recurrent myocardial infarction, and stroke. Follow-up will be censored at time of study withdrawal or last known alive. The time-to-first MACE event up to one year post-discharge will be compared between intervention and control arms. Cumulative incidence rates will presented as Kaplan-Meier curves and in tables for 30 days, 6 months, and 1 year post-discharge. The primary analysis will be a Cox proportional hazards model accounting for within hospital clustering using robust standard errors and adjustment for selected patient characteristics (Section 8.3.1) which includes a propensity score for intervention. We will use the same propensity score described in section 3.1. Cluster heterogeneity will be quantified using ICCs calculated from unadjusted and adjusted models. We will calculate the ICCs across all hospitals and also by treatment group.

After Steering Committee consensus, the randomization scheme was changed from 1:1 to 2:1 Usual Care vs. Intervention effective November 16, 2015. Randomization schema was added as a covariate for adjustment as shown in Section 8.3.1 and to the propensity model as shown in Section 8.3.2.

4. Secondary Endpoints

4.1 Medication Selection at discharge

Inclusion Criteria: All patients.

We will use logistic regression with GEE to account for within hospital clustering to evaluate whether copayment intervention is associated with discharge $P2Y_{12}$ inhibitor type. We will use the same methods for adjustment as in the primary analysis.

4.2 Non-persistence with antiplatelet therapy at 1 year

Non-persistence or death vs. persistence at 1 year

Analogous to Section 3.1, we will examine the outcome of death or non-persistence; non-persistence still defined as interruption ≥30 days of $P2Y_{12}$ receptor inhibitor. The primary analysis will be a logistic regression model with generalized estimating equations (GEE) to account for within hospital clustering and adjustment for selected patient characteristics (Section 8.3.1) and a propensity score for intervention (Section 8.3.2). We will use the same propensity score described in section 3.1. Cluster heterogeneity will be quantified using ICCs calculated from unadjusted and adjusted models. We will calculate the ICCs across all hospitals and also by treatment group.

Non-persistence to initial $P2Y_{12}$ receptor inhibitor at 1 year

Analogous to Section 3.1, we will use the LOCF method for patients who died before one year or had missing 1 year $P2Y_{12}$ inhibitor status. Patients who have continued their initial $P2Y_{12}$ receptor inhibitor use at one year from discharge with less than 30 continuous days of interruption will be considered persistent. Patients who switched from their initial $P2Y_{12}$ receptor inhibitor will be considered non-persistent.

The primary analysis will be a logistic regression model with generalized estimating equations (GEE) to account for within hospital clustering and adjustment for selected patient characteristics (Section 8.3.1) and a propensity score for intervention (Section 8.3.2). We will use the same propensity score described in section 3.1. Cluster heterogeneity will be quantified using ICCs calculated from unadjusted and adjusted models. We will calculate the ICCs across all hospitals and also by treatment group.

4.3 Medication fill using pharmacy data only

Inclusion Criteria: Patients with pharmacy data collected.

Persistence:

Using pharmacy data, we will calculate persistence using the same definition as in the primary analysis with non-persistence defined as a fill gap ≥30 days. Analogous to Section 3.1, we will use the LOCF method for patients who died before one year or had missing 1 year $P2Y_{12}$ status. Persistence at 1 year will be compared by copayment intervention using logistic regression with GEE to account for within hospital clustering and the same methods for adjustment as in the primary analysis.

Adherence:
Using pharmacy data, we will calculate the proportion of days covered. Patients with proportion of days covered ≥80% of expected prescriptions over one year of follow-up or until death date will be considered adherent. Adherence at 1 year will be compared by copayment intervention using logistic regression with GEE to account for within hospital clustering and the same methods for adjustment as in the primary analysis.

4.4 Medication Drug Levels

Inclusion Criteria: All patients with valid drug level data.

A subset of patients will have blood drawn over the one year of follow-up after AMI. This blood draw will be randomly assigned to 250 patients (125 in each arm) at each of the following follow-up time points: 3, 6, 9, or 12 months. Drug levels or metabolites of clopidogrel or ticagrelor will be measured, as appropriate. Persistence (yes vs. no) will be defined based on clinically selected cut-offs of minimum drug levels. Medication drug level data will be presented in Table 6 in Section 8.2.1.

4.5 Comparison of Medication Use from different sources

Overall and stratified by copayment reduction, we will assess agreement among patient reported medication use, medication fill adherence, and drug levels using Kappa statistics and summarize using frequencies and percentages (Table 7 in Section 8.2.1).

4.6 Cost

A detailed description of the healthcare resource utilization endpoints and analysis will be contained in a separate SAP, drafted following and guided by the primary clinical endpoint results.

4.7 Safety – Bleeding

Bleeding events will be collected using the Bleeding Academic Research Consortium (BARC) bleeding definition. Additionally, the severity of bleeding will be categorized using the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) definition for severe, moderate, or mild bleeding. We will assess the effect of copayment reduction on bleeding using the same methods as the composite MACE outcome.

4.8 Unplanned Revascularization

We will assess the effect of copayment reduction on unplanned revascularization using the same methods as the composite MACE outcome.

4.9 Components of MACE

We will assess the effect of copayment reduction on each component of MACE using the same methods as the composite MACE outcome.

4.10 MACE plus unplanned revascularization

We will assess the effect of copayment reduction on the composite of all-cause death, recurrent MI, stroke, and unplanned revascularization using the same methods as the composite MACE outcome.

4.11 Cardiovascular Mortality

We will assess the effect of copayment reduction on cardiovascular mortality using the same methods as the composite MACE outcome.

4.12 As Treated Analysis

We will conduct an as treated analysis of the co-primary endpoints by excluding intervention patients who did not use the voucher during any of the 12 months of follow-up. We will use the same methods as described in Section 3.1 and 3.2, but we will re-fit the propensity score among this population. All tables included in Section 8.2.1 with the exception of Table 1 will be repeated for this subset of patients.

4.13 Exploratory Analysis

Reduction of the co-primary endpoint of MACE could be driven by several factors including improved adherence to therapy, increasing use of a higher-potency $P2Y_{12}$ receptor inhibitor, or both. Exploratory analyses will examine the associations of these two factors with MACE. In addition, instrumental variable analyses will be considered for the co-primary endpoints.

5. Subgroups

We will conduct subgroup analyses (Tables 3b, 4b, and 9b) for the following subgroups using the same methods as the primary analysis with the addition of the main effect for subgroup and an interaction term for subgroup by intervention. Indicator variables for the subgroups will be included in the propensity model for all subgroups except initial treatment selection.

- Age: Age ≥65 and age <65
- Sex: Males and females
- Insurance status: private and non-private
- Race: White and non-White
- STEMI and NSTEMI
- In-hospital PCI and no in-hospital PCI

6. Secondary Analysis of Primary Endpoints

6.1 Non-persistence with antiplatelet therapy at 1 year

Propensity matched analysis: Within each of the four randomization strata defined, using medians across potential sites from survey conducted prior to ARTEMIS, by high (≥400) vs. low (<400) annual site AMI volume and high (≥15%) vs. low (<15%) proportion of ticagrelor use and by randomization scheme (2:1 vs. 1:1), we will match intervention arm patients to usual care patients. Matching within randomization scheme and strata forces matches across sites of similar size and proportion ticagrelor use and time of site randomization. To run the computerized

matching of intervention to usual care patients, we will utilize the gmatch macro publicly available from the Mayo Clinic Division of Biomedical Statistics and Informatics website of locally written SAS macros. This macro was downloaded on 5/13/13 from the following website: http://mayoresearch.mayo.edu/mayo/research/biostat/sasmacros.cfm. The gmatch macro performs greedy matching of cases to controls (intervention patients to usual care patients) within a pre-specified caliper. Greedy matching starts by creating two pools of patients; 1 pool for intervention patients and 1 pool for usual care. Each pool is randomly sorted, then for each intervention patient, we select the first usual care patient in the randomly sorted pool that has a propensity score within the pre-specified caliper. Once a match is made, it is never broken even if another closer match exists. Patients will be matched based on the propensity for intervention group using the propensity score estimated in the primary analysis. If there are no usual care patients with a propensity score within the caliper of a given intervention patient then that intervention patient is not included in the matched sample. We will match on the logit of the propensity score and use a caliper with a width of 0.2 times the standard deviation of the logit of the propensity score as suggested by Austin [7]. To estimate the intervention effect on non-persistence among the propensity matched sample we will fit a logistic regression model stratified by matched pair. Matching on the propensity score is expected to reduce most of the observed differences in patient case mix between the two groups so further adjustment is not necessary.

Random Intercepts for Hospital: We will fit a logistic regression model with adjustment for the same selected patient characteristics and same propensity score as in the primary analysis. The only modification is that we will account for within hospital clustering using random intercepts for hospitals instead of GEE.

6.2 MACE

Propensity matched analysis: We will use the same matched sample described in section 6.1 to estimate the intervention effect on MACE using a Cox proportional hazards model stratified by matched pair.

Random Intercepts for Hospital: We will fit a Cox proportional hazards model with adjustment for the same selected patient characteristics and same propensity score as in the primary analysis. The only modification is that we will account for within hospital clustering using random intercepts for hospitals instead of robust standard errors.

7. References

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8. Appendices

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8.2 Appendix: Table Shells

8.2.1 Main Table Shells

Table 1: Site Characteristics by Copayment Intervention

	Overall (N=)	Copayment Intervention (N=)	Usual Care (N=)
N patients enrolled			
MI volume			
% high (≥400) MI volume			
Site % baseline ticagrelor use			
% high (≥15%) baseline ticagrelor use			
Region			
Randomization scheme			
Total bed size			
Teaching status			
Government hospital			
Member of a healthcare network			
Surgery capabilities			

Table 2a: Patient Level Baseline Characteristics by Copayment Intervention

	Overall (N=patients)	Copayment Intervention (N=patients)	Usual Care (N=patients)
Age			
Gender, % male			
Non-white race			
Hispanic ethnicity			
Private insurance			
Prior MI			
Prior PCI			
Prior CABG			
Prior stroke/TIA			
Prior heart failure			
Dialysis			
PAD			
Hypertension			
Diabetes			
Current/recent smoker			
Weight			
Transfer in			
STEMI			
Home P2Y12 inhibitor			
Home aspirin			
Creatinine Clearance			
Nadir hemoglobin			
Multivessel disease			
Access Site			
PCI performed			
CABG performed			
Drug-eluting stent			
In-hospital or prior bleeding			
In-hospital MI			
In-hospital stroke			
Cardiogenic shock (Killip IV on presentation or in-hospital cardiogenic shock)			

Heart failure (Killip II/III on presentation or in-hospital heart failure)			
Cardiac Arrest			
Health Literacy			
Baseline angina frequency			
Cardiac Rehab			
Baseline PHQ2>3			
Baseline EQ5D VAS			
Married			
Employed			
Education (college graduate)			
Baseline financial hardship			
Missed >1 dose of medication in the last month			

Table 2b: Cluster Level Summary Data of Baseline Characteristics by Copayment Intervention

	Overall (N=sites)	Copayment Intervention (N=sites)	Usual Care (N=sites)
Randomization Scheme			
Site MI volume			
Site % Ticagrelor			
Age			
Gender, % male			
Non-white race			
Hispanic ethnicity			
Private insurance			
Prior MI			
Prior PCI			
Prior CABG			
Prior stroke/TIA			
Prior Heart Failure			
Dialysis			
PAD			
Hypertension			
Diabetes			
Current/recent smoker			
Weight			
Transfer in			
STEMI			
Home $P2Y_{12}$ inhibitor			
Home aspirin			
Creatinine Clearance			
Nadir hemoglobin			
Multivessel disease			
Access Site			
PCI performed			
CABG performed			
Bare Metal Stent			
In-hospital or prior bleeding			
In-hospital MI			
In-hospital stroke			

Cardiogenic shock (Killip IV on presentation or in-hospital cardiogenic shock)			
Heart failure (Killip II/III on presentation or in-hospital heart failure)			
Cardiac Arrest			
Health Literacy			
Baseline angina frequency			
Cardiac Rehab			
Baseline PHQ2>3			
Baseline EQ5D VAS			
Married			
Employed			
Education (college graduate)			
Baseline financial hardship			
Missed >1 dose of medication in the last month			

Table 3a: Clinical Outcomes by Copayment Intervention

	Cumulative Incidence at 12 months (95% CI)			Unadjusted		Adjusted	
Outcome	Overall (N=)	Copayment Intervention (N=)	Usual Care (N=)	HR (95% CI)	P-value	HR (95% CI)	P-value
MACE							
All-cause death							
MI							
Stroke							
BARC 2+ bleed							
BARC 3+ bleed							
GUSTO Moderate/Severe Bleed							
Unplanned Revascularization							
MACE + unplanned revascularization							
Cardiovascular death							

Table 3b: Subgroup Analysis of MACE by Copayment Intervention

	Cumulative Incidence at 12 months (95% CI)			Unadjusted		Adjusted	
Subgroup	Overall (N=)	Copayment Intervention (N=)	Usual Care (N=)	HR (95% CI)	P-value	HR (95% CI)	P-value
Age							
≥65							
<65							
Sex							
Male							
Female							
Insurance type							
Private							
Non-private							
Race							
White							
Non-white							
MI type							
STEMI							
NSTEMI							
In-hospital PCI							
In-hospital PCI							
No in-hospital PCI							

Table 4a. Medication Non-Persistence by Copayment Intervention

	Persistence at 12 months			Unadjusted		Adjusted	
Outcome	Overall (N=)	Copayment Intervention (N=)	Usual Care (N=)	OR (95% CI)	P-value	OR (95% CI)	P-value
Non-persistence to any $P2Y_{12}$ vs. persistence							
Non-persistence or mortality to any $P2Y_{12}$ vs. persistence							
Non-persistence to initial $P2Y_{12}$ vs. persistence							

Table 4b.Subgroup Analysis of Medication Non-Persistence to Any $P2Y_{12}$ by Copayment Intervention

	Persistence at 12 months			Unadjusted		Adjusted	
Subgroup	Overall (N=)	Copayment Intervention (N=)	Usual Care (N=)	OR (95% CI)	P-value	OR (95% CI)	P-value
Age							
≥65							
<65							
Sex							
Male							
Female							
Insurance type							
Private							
Non-private							
Race							
White							
Non-white							
MI type							
STEMI							
NSTEMI							
In-hospital PCI							
In-hospital PCI							
No in-hospital PCI							

Table 5. ICCs

	Overall		Copayment Intervention		Usual Care	
	Unadjusted ICC	Adjusted ICC	Unadjusted ICC	Adjusted ICC	Unadjusted ICC	Adjusted ICC
MACE at 1 year						
Non-persistence to any $P2Y_{12}$ vs. persistence						
Medication Selection at discharge						

Table 6. Medication Use by Patient Reported Persistence and Copayment Intervention in Substudies

	Overall (N=X patients)		Copayment Intervention (N=X patients)		Usual Care (N=X patients)	
Persistence Measure	Persistent	Not Persistent	Persistent	Not Persistent	Persistent	Not Persistent
$P2Y_{12}$ Fill Persistence by 1 year						
$P2Y_{12}$ Fill Adherence by 1 year						
Drug levels at 1 year						
Drug levels at 3 months						
Drug levels at 6 months						
Drug levels at 9 months						

Table 7. Kappa Statistics for Assessing Agreement with Patient reported persistence to any $P2Y_{12}$ at 1 year

	Overall (N=X patients)		Copayment Intervention (N=X patients)		Usual Care (N=X patients)	
Persistence Measure	Kappa (95% CI)	P-value*	Kappa (95% CI)	P-value*	Kappa (95% CI)	P-value*
$P2Y_{12}$ Fill Persistence by 1 year						
$P2Y_{12}$ Fill Adherence by 1 year						
Drug levels at 1 year						
Drug levels at 3 months						
Drug levels at 6 months						
Drug levels at 9 months						

*P-values are for test of Kappa = 0 (no more agreement than expected by chance).

8.2.2 Supplementary Table Shells

Table 8: Longitudinal Patterns of $P2Y_{12}$ use

	Overall (N=patients)	Copayment Intervention (N=patients)	Usual Care (N=patients)
Overall Duration of any $P2Y_{12}$			
Duration of initial $P2Y_{12}$			
Summed duration of initial $P2Y_{12}$			

Table 9a: Kaplan-Meier Cumulative Incidence

	Overall (N=X patients)			Copayment Intervention (N=X patients)			Usual Care (N=X patients)		
Outcome Time (days)*	KM rate (95% CI)	N remaining	N events	KM rate (95% CI)	N remaining	N events	KM rate (95% CI)	N remaining	N events
MACE									
30									
180									
365									
All-cause death									
30									
180									
365									
MI									
30									
180									
365									
Stroke									
30									
180									
365									
BARC 2+ bleed									
30									
180									
365									
BARC 3+ bleed									
30									
180									
365									
GUSTO Moderate/Severe Bleed									
30									
180									
365									
Unplanned Revascularization									
30									
180									
365									
Cardiovascular death									
30									

180 365									
MACE+Unplanned Revascularization 30 180 365									

*Time (days) from discharge

Table 9b: Kaplan-Meier Cumulative Incidence of MACE among Subgroups

	Overall (N=X patients)	Copayment Intervention (N=X patients)			Usual Care (N=X patients)		
Subgroup Time (days)*	N events	KM rate (95% CI)	N remaining	N events	KM rate (95% CI)	N remaining	N events
Age>=65: 30 180 365							
Age<65: 30 180 365							
Male: 30 180 365							
Female: 30 180 365							
Private Insurance: 30 180 365							
Government Insurance: 30 180 365							
White: 30 180 365							
Non-white: 30							

180 365							
STEMI: 30 180 365							
NSTEMI: 30 180 365							
In-hosp PCI: 30 180 365							
No In-hosp PCI: 30 180 365							

*Time (days) from discharge

8.3 Appendix: List of Adjustment Variables

8.3.1 Adjustment Variables for Primary Models

Variable	Variable Type
Intervention	Yes/no
Randomization scheme	Categorical (2:1 vs. 1:1 scheme)
Interaction* between intervention and randomization scheme	Categorical
Site MI volume	Categorical (high vs. low)
Site % Ticagrelor use	Categorical (high vs. low)
Age	Continuous
Male gender	Yes/no
Race	Categorical (white vs. nonwhite)
Insurance Payors	Categorical (private vs. non-private)
Region	Categorical (Northeast, West, South, vs. Midwest)
Propensity for intervention	Continuous

*We will test for significant interaction and will drop if the interaction term is not significant.

8.3.2 Variables for Propensity Score Model

Variable	Variable Type
Randomization scheme	Categorical (2:1 vs. 1:1 scheme)
Age	Continuous
Age >=65 vs. <65	Yes/no
Male gender	Yes/no
Race	Categorical (white vs. nonwhite)
Ethnicity	Categorical (Hispanic vs. non-Hispanic)
Insurance Payors	Categorical (private vs. non-private)
Prior MI	Yes/no
Prior PCI	Yes/no
Prior CABG	Yes/no
Prior stroke/TIA	Yes/no
Prior Heart failure	Yes/no
Dialysis	Yes/no
PAD	Yes/no
Hypertension	Yes/no
Diabetes	Yes/no
Current/recent smoker	Yes/no
Weight	Continuous
Transfer in	Yes/no
STEMI	Yes/no
Home $P2Y_{12}$ inhibitor	Yes/no
Home aspirin	Yes/no
Creatinine Clearance	Continuous
Nadir hemoglobin	Continuous
Multivessel disease	Yes/no
Access Site	Categorical (Femoral vs. other)
PCI performed	Categorical (multivessel vs. culprit vs. none)
CABG performed	Yes/no
Drug-eluting stent implanted	Yes/no
In-hospital or prior bleeding	Yes/no
In-hospital MI	Yes/no
In-hospital stroke	Yes/no
Cardiogenic shock (Killip IV on presentation or in-hospital cardiogenic shock)	Yes/no
Heart failure (Killip II/III on presentation or in-hospital heart failure)	Yes/no
Cardiac Arrest	Yes/no
Cardiac Rehab Referral	Yes/no
Health Literacy	Yes/no (score>=10 vs. <10)
Baseline angina frequency	Categorical (100 vs. 70-90 vs. 0-60 points)
Baseline PHQ2>3	Categorical
Baseline EQ5D VAS	Continuous

Married	Yes/no
Employed	Yes/no
Education (college graduate)	Yes/no
Baseline financial hardship	Categorical (1 vs. 2/3 vs. 4/5)
Missed >1 dose of medication in the last month	Yes/no
Site: Total bed size	Continuous
Site: Teaching Status	Yes/no
Site: Government hospital	Yes/no
Site: Member of a Healthcare Network	Yes/no
Site: Surgery Capabilities	Yes/no

8.4 Appendix: Figure Shells

Figure 1: Consort Diagram

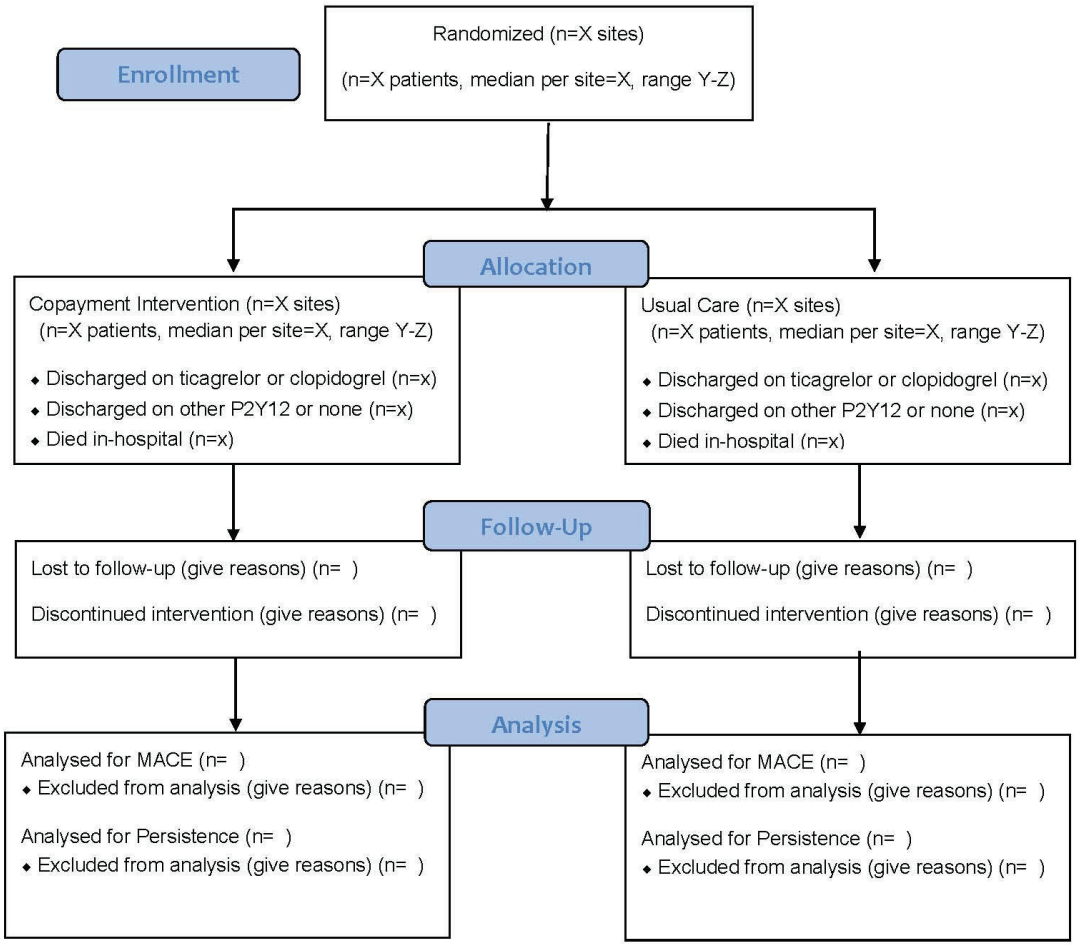

Figure 2a: Consort Diagram under 1:1 randomization

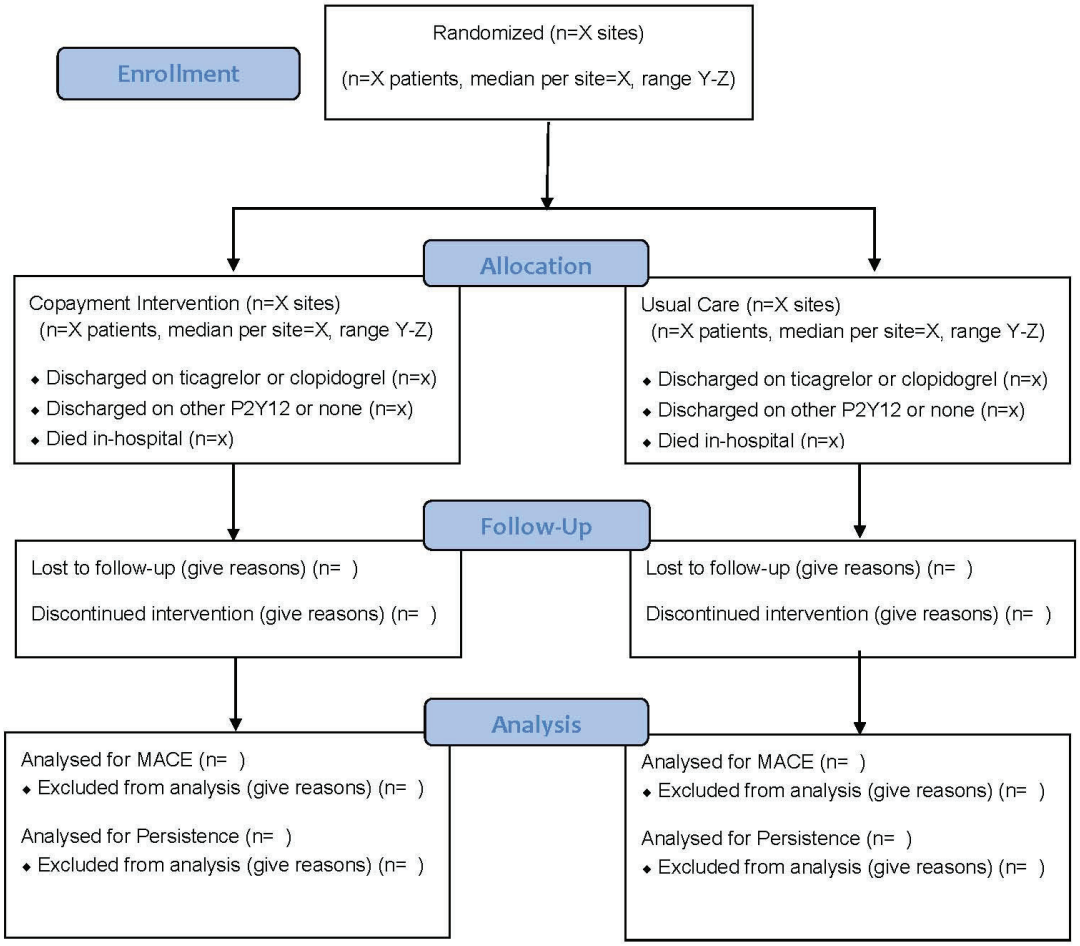

Figure 2b: Consort Diagram under 2:1 randomization