ARTEMIS

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

Study Protocol

D5130R00030

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[confidential]

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1. Background

1.1. Antiplatelet therapy after acute myocardial infarction

Dual antiplatelet therapy with aspirin, combined with a $P2Y_{12}$ receptor inhibitor, is a cornerstone of therapy for acute myocardial infarction (AMI). Treatment with clopidogrel in addition to aspirin resulted in a 20% reduction in major adverse cardiovascular events (MACE) when compared with aspirin alone among all patients with non–ST-elevation acute coronary syndrome, regardless of revascularization strategy [1, 2]. The Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial and the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) extended these results to patients with ST-segment elevation myocardial infarction (STEMI) [3, 4]. More potent inhibition of the $P2Y_{12}$ receptor has led to a further reduction in clinical events. In the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial, patients receiving ticagrelor had a 16% lower risk of the composite endpoint of cardiovascular death, AMI, and stroke compared with clopidogrel-treated patients [5]. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) study also demonstrated similar lowering of cardiovascular events with prasugrel compared to clopidogrel in AMI patients undergoing percutaneous coronary intervention (PCI) [6], but had no significant benefit among non-revascularized patients [7]. Compared with clopidogrel, the use of ticagrelor and prasugrel, which are both higher potency $P2Y_{12}$ receptor inhibitors, has resulted in a greater risk of bleeding.

Current guidelines for the management of STEMI [8] and non-STEMI (NSTEMI) [9] recommend treatment with a $P2Y_{12}$ receptor inhibitor for up to one-year post-AMI. Despite these recommendations, only 74% of AMI patients are currently prescribed a $P2Y_{12}$ receptor inhibitor at discharge [10]. Rates of $P2Y_{12}$ receptor inhibitor use are higher among patients treated with PCI [11], but rates are only approximately 50% for medically treated patients [12, 13]. Prasugrel and ticagrelor received regulatory approval in 2009 and 2011, respectively, and clopidogrel became available in generic formulation in 2012. Current guidelines recommend any of these three medications as first-line agents for PCI-treated AMI patients, and either clopidogrel or ticagrelor for AMI patients treated with a non-invasive strategy. Recent observational data revealed that clopidogrel is the most commonly prescribed $P2Y_{12}$ receptor inhibitor [14]. Yet long-term adherence to cardiovascular medications, including $P2Y_{12}$ receptor inhibitor therapy, is suboptimal [15-17], and disruption of planned antiplatelet therapy has been associated with worse clinical outcomes [16, 18, 19].

1.2. Cost sharing, clinician choice of antiplatelet agent, and long-term medication adherence

Most health plans have cost-sharing strategies with tiered copayment plans that apply different patient copayment amounts for medication brands that are generic, preferred, and non-preferred. The purpose of these cost-sharing strategies is to provide incentives to use generic or lower-cost medications. In observational studies, increased out-of-pocket medication expenses have been associated with lower rates of treatment, delays to treatment, lower medication adherence, and higher drug discontinuation rates [20-24]. Lower income and older patients are at greater risk of cost-related medication nonadherence [25, 26]. Health plan changes that moved brand medications to a lower copay tier have been associated with improved adherence [27]. Therefore,

copayment reduction is a potential strategy to improve medication adherence and address disparities in cardiovascular outcomes.

The Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) study randomized post-AMI patients to either usual prescription coverage or full coverage for all prescription costs. Rates of adherence to secondary prevention therapies were 4–6% higher among the full coverage group [28]. There was no significant difference in clinical outcomes for the full study population, but non-white patients had a lower incidence of vascular events and revascularization when provided with full medication coverage [29]. Nevertheless, the incentive being tested was imperfect, since the drugs that were evaluated may have already been associated with low copayments and there was a median delay of 49 days post-discharge before drug coverage began (therefore, missing the time period when many patients self-discontinue medications).

Most clinicians do not prescribe exclusively generic or branded medication for common cardiovascular classes such as statins, beta-blockers, and angiotensin-converting enzyme inhibitors [30]. Perceived medication cost to the patient may influence clinician choice of $P2Y_{12}$ receptor inhibitor during hospitalization for AMI. Switching from a one-tier to a three-tiered copay system leads to increased utilization of medications with the lowest copay [31, 32], presumably due to patient and/or clinician preference to utilize the drug with the lowest out-of-pocket expenditure. What is unclear is whether or not the cost burden to the patient, as perceived by the clinician, influences the choice of the antiplatelet agent prescribed. Whether or not greater patient affordability will lead to improved antiplatelet therapy adherence and improved cardiovascular outcomes is also unknown.

2. Study Objectives

Current patterns of $P2Y_{12}$ receptor inhibitor use provide an excellent opportunity to test the impact of copayment reduction on clinician choice of medication, patient adherence, and clinical outcomes. The Affordability and Real-world Antiplatelet Treatment Effectiveness After Myocardial Infarction Study (ARTEMIS) trial is a practical multicenter cluster-randomized clinical trial that will assess the impact of copayment reduction, by equalizing the copayments for clopidogrel and ticagrelor. ARTEMIS will assess prescribing patterns, patient medication adherence, and clinical outcomes up to one year. We hypothesize that reducing out-of-pocket costs for a $P2Y_{12}$ receptor inhibitor will lead to improved medication adherence. Additionally, copayment reduction of both generic and brand antiplatelet agents may lead to a reduction in MACE risk, partly due to the selection of a more potent antiplatelet agent has been shown to reduce MACE in randomized clinical trials, and partly due to greater patient adherence to an evidence-based secondary prevention medication. By reducing out-of-pocket patient cost for both generic and non-generic treatment options, we hypothesize that the choice of antiplatelet therapy will primarily be driven by risk-benefit assessment, rather than the cost burden to the patient, leading to a change in prescribing patterns.

The co-primary objectives of ARTEMIS are the following:

1. To determine if patient copayment reduction leads to lower risk of MACE (composite of death, AMI, and stroke) at one year after discharge.
2. To determine if patient copayment reduction leads to higher long-term persistence of any $P2Y_{12}$ receptor inhibitor at one year after discharge.

Secondary objectives are:

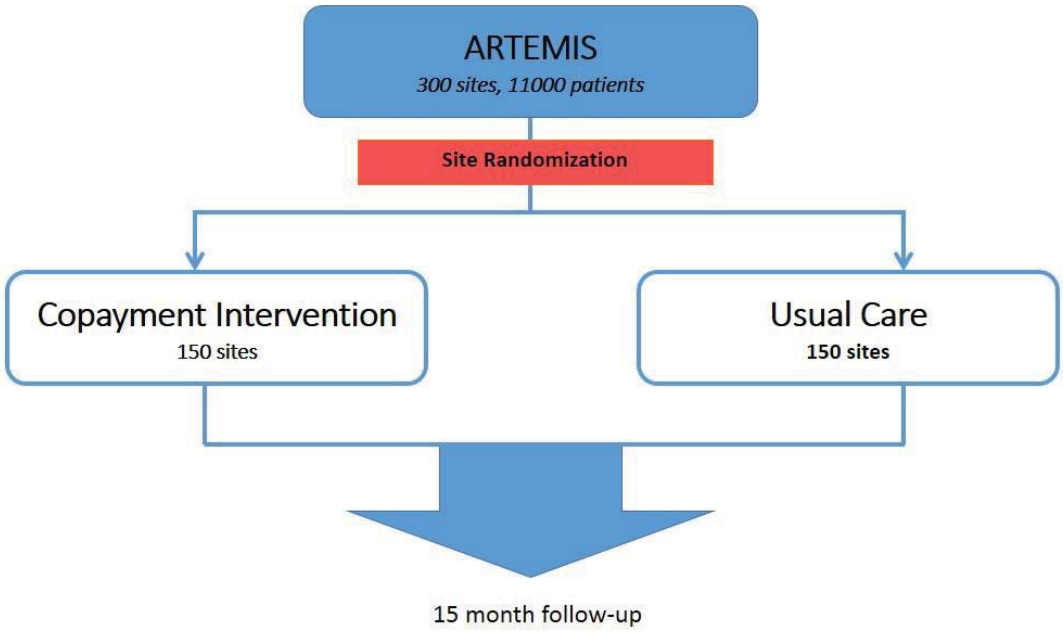
3. To evaluate whether reducing patient copayments for both generic and brand $P2Y_{12}$ receptor inhibitor options affects medication selection at discharge.
4. To assess the impact of copayment reduction on the total cost of health care for patients after AMI.

3. Study Design

3.1. Overview

ARTEMIS is a prospective cluster-randomized clinical trial that will evaluate whether patient copayment reduction significantly influences antiplatelet therapy selection and long-term adherence. This study will also examine patient outcomes and the overall cost of care after AMI. Approximately 11,000 patients with STEMI or NSTEMI will be enrolled at approximately 300 hospitals. Study sites selected for ARTEMIS will be geographically diverse, and will represent a variety of hospital types and capabilities (e.g., teaching hospital, community hospital, etc.). After institutional review board (IRB) approval of the study, each hospital will be randomized into either the intervention or the control arm. Hospitals randomized to the intervention arm will have the opportunity to offer enrolled patients either clopidogrel (generic $P2Y_{12}$ receptor inhibitor option) or ticagrelor (brand $P2Y_{12}$ receptor inhibitor option) without patient copayment contribution in the 12 months post-index AMI discharge. Hospitals in the control arm will provide care, per usual clinical routine. Notably, for both the intervention and control arms, all patient management decisions (including the choice of antiplatelet therapy) are completely subject to the discretion of the care providers. The duration of antiplatelet therapy, including treatment beyond 12 months, will also be at the discretion of care providers. Primary and secondary endpoints will be assessed at 12 months. We will assess trends in antiplatelet medication use and clinical events after discontinuation of the copayment intervention for an additional three months of follow-up. Centralized follow-up will be conducted every three months via telephone or web-based contact by the Duke Clinical Research Institute (DCRI). The study design is illustrated in Figure 1.

Figure 1. Study Design



3.2. 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

3.3. 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

3.4. Study Interventions

After IRB approval, each site will be randomly assigned to either the intervention or the control arm. Randomization will be stratified by annual site AMI volume and the proportion of ticagrelor use at each site.

For hospitals randomized to the control arm, all patients receive usual care and no study intervention is performed. For hospitals randomized to the intervention arm, the selection and duration of antiplatelet medication use, as in the usual care arm, will be directed by the patient's health care provider(s). Each study patient will be provided a voucher card at study enrollment. This voucher card can be used at any pharmacy to offset any patient copayments for the filling of any prescriptions of clopidogrel or ticagrelor. If a patient loses prescription drug coverage during the follow-up period, the voucher card can be used to cover the entire cost of clopidogrel or ticagrelor. Similarly, for Medicare/Medicaid-insured patients, the voucher will offset the entire prescription cost of clopidogrel or ticagrelor. This card can be used to fill 30-day or 90-day prescriptions of clopidogrel or ticagrelor, and can be used multiple times up to a 12-month supply, as directed by the patient's care provider. Patients will be notified prior to the completion of the copayment intervention at 12 months to permit planning for continued dual antiplatelet therapy if recommended by the care provider. Copayment assistance will not be provided if antiplatelet therapy is continued beyond 12 months.

3.5. Baseline Data Collection

Details of the index hospitalization will be collected by participating sites for each enrolled patient via an electronic data collection tool managed by DCRI, which can be accessed via a secure password-protected web-based data entry system. The following patient data will be collected:

- Sociodemographic data
- Medical history and comorbidities
- Presentation characteristics (e.g., cardiac biomarkers, ECG findings, symptoms or signs of cardiogenic shock)
- In-hospital and discharge medications
- Angiographic and procedural characteristics, such as extent and severity of coronary artery disease, lesion location, type of stent(s)
- In-hospital events (e.g., bleeding, recurrent AMI)

- Discharge $P2Y_{12}$ receptor inhibitor use (e.g., dose, planned duration of therapy, planned switching)
- Resource use and medical costs (e.g., collection of uniform billing forms [UB-04] and detailed itemized bill forms)
- Patient-reported outcomes (e.g., depression symptoms, prior medication adherence [Morisky questionnaire])

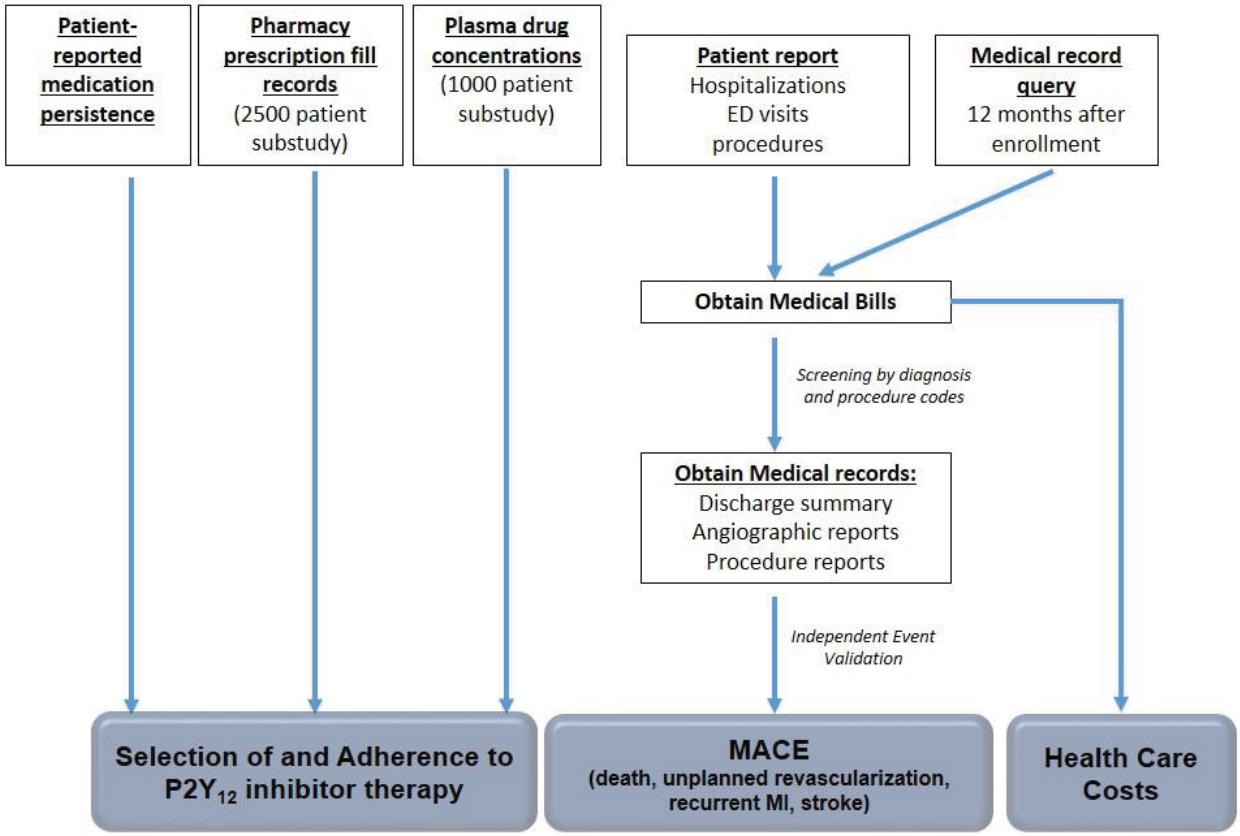
Finally, sites will be surveyed to collect institutional practices on peridischarge and transition of care processes that can influence antiplatelet therapy selection and adherence.

3.6. Follow-up Data Collection

After index discharge, longitudinal information on patient treatment ($P2Y_{12}$ receptor inhibitor use and concomitant medications), effectiveness and safety outcomes, and resource use will be collected. Follow-up will occur every three months post-discharge via a centralized telephone interview conducted by trained personnel at the DCRI or a web-based survey based on patient preference and feasibility. This centralized approach will maximize the consistency and quality of data collection and minimize loss to follow-up. If web-based data collection is incomplete, then the DCRI will follow-up with the patient via telephone to minimize missing data. At each interview, patients will be asked to report current medications, interval rehospitalizations, and health status.

Based on patient-reported events, medical billing data for these hospitalizations, emergency department visits, and procedures will be obtained. The UB-04 claims form represents a common reporting format that all United States hospitals use; this form contains a number of important data items, including International Classification of Diseases, Ninth Revision (ICD-9) diagnosis and procedure codes which can be used to identify major events and procedures that occurred during each admission. For facilities that do not produce UB-04s (e.g., Veterans Administration hospitals), length of stay, along with other case report resource variables, will be collected. This step establishes the first line of screening for effectiveness and safety endpoints. Based on billed diagnoses or procedures, if a MACE or bleeding event is suspected, additional collection of relevant hospital discharge summaries, angiographic, or procedural reports will be performed and independently reviewed by a study physician to validate patient-reported outcomes. Physicians performing event validations will be blinded to the intervention arm assignment (copayment reduction vs. usual care) of the participating hospitals. For a subset of 2500 randomly-selected patients, pharmacy records for $P2Y_{12}$ receptor inhibitor prescription fills will be obtained to validate patient-reported persistence. Figure 2 illustrates the process for identifying and validating effectiveness and safety endpoints.

Figure 2. Event Assessment



As an additional mechanism to safeguard against event under-reporting or loss to follow-up, sites will conduct a medical record query 12 months after the last enrolled patient to screen for any hospitalizations or procedures. If any unreported events are found, then billing data, discharge summaries, and procedure reports will be collected for endpoint validation, as described previously. Finally, contact information for the next-of-kin (or other emergency contact) and consent to contact will be obtained at enrollment. This will provide an additional means to prevent loss to follow-up.

3.6. Blood Collection

A total of 1000 patients (500 in each arm) will be randomly selected for blood sampling to assess $P2Y_{12}$ receptor inhibitor drug levels at 3, 6, 9, and 12 months after discharge (250 patients at each time point). Consent for blood draws will be obtained at enrollment. The DCRI will contact patients and provide collection kits for blood sampling to be done locally. Plasma concentrations of each drug (clopidogrel, ticagrelor, or prasugrel) and the active metabolite of clopidogrel will be measured by liquid chromatography with mass spectrometry. These pharmacokinetic results will be correlated with patient-reported persistence to $P2Y_{12}$ receptor inhibitor therapy.

4. Study Endpoints

4.1. Event Definitions

Each event will be independently validated by study physicians using the following definitions:

- **MACE:** Defined as a composite of all-cause death, myocardial infarction, and stroke
- **All-cause death**: Defined as death due to any reason
- **Cardiovascular death**: Includes any one of the following:
    - Death by any mechanism (arrhythmia, heart failure, shock) related to and within 30 days after an AMI, including death resulting from a procedure (e.g., PCI or coronary artery bypass grafting [CABG]) used to treat the AMI
    - Sudden cardiac death (unwitnessed sudden death without any evidence of a specific cause of death may be classified as sudden cardiac death)
    - Death due to heart failure or cardiogenic shock
    - Death due to stroke (death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication from the stroke)
    - Death due to other cardiovascular causes (e.g., dysrhythmia, pulmonary embolism, cardiovascular intervention, aortic aneurysm rupture, peripheral arterial disease, mortal complications of cardiac surgery or non-surgical revascularization)
- **Myocardial infarction:** A rise/fall of cardiac biomarkers (troponin I, troponin T, or creatine kinase MB) with at least one value above the institutional upper limit of normal associated with at least one of the following:
    - Symptoms of ischemia
    - New (or presumed new) ST-segment or T-wave changes, or left bundle branch block
    - Development of pathologic Q-waves on the ECG
    - Imaging evidence of new loss of myocardium or new wall motion abnormality
    - Identification of intracoronary thrombus by angiography or autopsy

  PCI-related AMI requires biomarker elevation >5 times the upper limit in patients with normal baseline values or a rise ≥20% if the baseline values are elevated. CABG-related AMI requires biomarker elevation ≥10 times the upper limit of normal. Periprocedural AMI requires at least one of the following:
    - Symptoms of myocardial ischemia
    - New ischemic ECG changes
    - Angiographic findings consistent with procedural complication
    - Imaging evidence of new loss of myocardium or new wall motion abnormality
- **Stroke:** Loss of neurological function caused by an ischemic or hemorrhagic event with residual symptoms at least 24 hours after onset or leading to death. Hemorrhagic stroke includes any nontraumatic, intraparenchymal, intraventricular, or subarachnoid hemorrhage.
- **Bleeding events:** Data on the date, time, severity, and location (including unidentifiable) of each bleeding event 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.

- **Medication persistence:** The co-primary endpoint of long-term persistence will be assessed using patient-reported medication persistence. Permanent and temporary discontinuation of a $P2Y_{12}$ receptor inhibitor will be queried at each follow-up interview. Patients who have continued $P2Y_{12}$ receptor inhibitor use at one year with less than 30 continuous days of interruption will be considered persistent. Validity of patient-reported persistence will be assessed using two complementary methods.
    - **Medication fill adherence:** A subset of patients (2500 per arm) will be randomly chosen for review of pharmacy data. Pharmacies will provide documentation of $P2Y_{12}$ inhibitor prescription fills at three-month intervals. Patients with proportion of days covered ≥80% of expected prescriptions over one year of follow-up will be considered adherent.
    - **Drug levels:** 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.
- **Unplanned coronary revascularization:** Any unplanned revascularization of one or more coronary vessels occurring after the index revascularization event. Staged coronary revascularizations that are planned at the time of the index procedure and completed within 60 days will not be considered an unplanned revascularization event, unless there is a documented recurrent ischemic episode determining the timing of the follow-up procedure.

4.2. Economic Data Collection

Index hospitalization resource use data will be collected on all patients using study case report forms and will be supplemented with UB-04 and detailed itemized hospitalization billing forms. These data will include length of stay (total and intensive care unit [ICU]), the occurrence of selected cardiac procedures (diagnostic cardiac catheterization, PCI/stent, and CABG), or any diagnostic and/or therapeutic procedure needed to evaluate and/or treat major bleeding complications.

The same resource use data will be collected post-discharge for each patient-reported emergency department visit, rehospitalization, or hospital-based procedure, as well as for any unreported visits or procedures identified by the enrolling hospital. Post-discharge UB-04 forms will be collected on all patients reporting a hospitalization, emergency department visit, or procedure. Hospital-specific Medicare Cost Report Ratio of Charges to Costs [33] will be requested for each visited facility. Two major types of medical costs will be assessed in this observational study: 1) hospital costs (including emergency department costs unassociated with hospital admission); and 2) physician service costs. Conversion of charges to costs using a top-down approach represents the state of the art for costing hospital-based care in United States multicenter cost studies [34-36]. To perform a charge to cost conversion on these bills, a UB-04 medical bill will be obtained for each hospitalization and emergency department visit. The revenue center categories and codes on the UB-04 will be matched against those in the hospital's most recent Medicare Cost Report to calculate revenue center-level costs, which will then be summed to yield total hospital costs. For physician service costs, major physician services will be enumerated directly from the case report forms and supplemented where necessary with the UB-04 hospital billing and procedure code data on procedures. Physician service costs will be assigned using the Medicare

Fee Schedule, which provides a standardized resource-based approach to costing out these services [37].

5. Statistical Methods

5.1. 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. 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%. 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. However, the sample size needs to be adjusted due to the cluster randomized design. We have applied the method described by Eldridge et al. [38] which accounts for the coefficient of variation (CV) of cluster size and the intra-cluster correlation (ICC). Prior multicenter studies have suggested an ICC of approximately 0.01 for the MACE endpoint. The CV of 0.65 has been suggested by others and can be guided by providing minimum and maximum enrollment at the site level [38]. 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 1. 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

The second 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. 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%. These calculations are based on the two group continuity corrected chi-square test statistic and assume that all observations are independently distributed. 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. 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. 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.

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 [39]. 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.

5.2. Statistical Analysis Plan

5.2.1. General Analytic Considerations

A detailed statistical analysis plan will be developed and contained in a separate document. Prior to analysis, study population details, including the number of sites randomized, the number of patients in each treatment arm, and the number of subjects lost to follow-up will be described. Data for all enrolled patients, regardless of whether or not they completed all protocol requirements, will be included for analysis.

Baseline comparisons of patient characteristics between intervention and control arms groups will be summarized as the mean; standard deviation; median; and 25^{th}, 75^{th} percentiles for continuous variables; and as counts and percentages for categorical variables. Differences in baseline characteristics between randomized groups will be compared using a Wilcoxon rank-

sum test for continuous variables and a chi-square test or the Fisher's exact test for categorical variables, adjusting for correlated responses within each site. All study objectives will be analyzed using intention-to-treat analyses.

5.2.2. Statistical Analyses for the Primary Objectives

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 cardiovascular death, recurrent myocardial infarction, and stroke. The time-to-first MACE event up to one year will be compared between intervention and control arms. Cox proportional hazard modeling will be applied to assess differences in risk of these events between groups after adjustment for patient demographic and baseline clinical characteristics. Events will be censored at the time of discontinuation from the study. The complete specification of adjustment variables will be described in the statistical analysis plan. Sensitivity analyses will be conducted with stratification on initial treatment selection.

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 alive at one year who remain on a $P2Y_{12}$ receptor inhibitor without interruption in treatment greater than 30 days. To compare the rate of persistence between intervention and control arms, multivariable logistic regression and Cox proportional hazards models with adjustment will be conducted using a subset of variables collected in the ARTEMIS study along with an indicator variable for the intervention arm group. General estimating equations will be applied to examine the impact of correlated responses within enrolling hospitals.

5.2.3. Statistical Analyses for the Secondary Objectives

Among secondary objectives, the first objective evaluates whether reducing patient copayments for both brand and generic antiplatelet therapy options affects medication selection at discharge. The study endpoint is discharge $P2Y_{12}$ receptor inhibitor type. Logistic regression with generalized estimating equations will be conducted to compare between groups with adjustment for correlation of response within site.

The second objective is to assess the impact of copayment reduction on the total cost of health care for patients after AMI. Analyses will be performed describing resource use and medical costs in patients according to treatment group: intervention versus control arm. Economic endpoints will include total medical costs for the index hospitalization, cumulative one-year medical costs, and cumulative MACE and bleeding costs. Calculation of medical cost differences will be presented without the costs of copayment reduction in order to identify the net costs and cost offsets produced by the intervention strategy. The source of cost savings and cost increases associated with copayment reduction will be explored. Of particular interest will be the costs associated with ischemic events due to MACE, rehospitalization due to AMI, unplanned coronary revascularization, and bleeding complications. A second set of calculations will present the same data with the copayment reduction costs included. To examine the interrelationships of baseline demographic and clinical characteristics with economic outcomes (such as total costs and length of stay), multivariable linear regression models will be employed. Medication use

patterns related to drug switching and levels of adherence will be examined for relationship with cumulative costs to the end of follow-up.

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.

5.2.3. Interim Analyses

An interim assessment will be conducted at one year after initiation of enrollment to ensure sample size requirements for the stated study objectives. No interim analyses of outcomes by intervention versus control group for the purpose of stopping the study prior to completion of enrollment are planned.

6. Patient Consent to Release Information and Ethical Considerations

6.1. Patient Consent to Release of Information

All randomization will occur at the site level, and no patient-level randomization will occur. The patient will provide authorization for the uses and disclosure of their personal health information as described in the study Consent to Release Information. This consent covers the collection and release of data regarding treatment and its outcomes for the entire period of the study. The confidential nature of patient information will be maintained.

6.2. Ethical Considerations

This study will be submitted to IRBs (local or central) for approval whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to IRBs and regulatory authorities as required by local laws and regulations. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with good clinical practices and applicable laws and regulations of the country or countries where the study is being conducted, as appropriate.

7. Study Operations and Oversight

Study operation management and scientific oversight for the ARTEMIS Study will be performed by the DCRI. Helpline support will be available from Monday–Friday, 8am–5pm Eastern Standard Time, to answer any study operational questions. Throughout the study, the DCRI will maintain call logs, documenting all issues and resolutions related to site assistance. All participating investigators and site staff will be provided the Helpline contact information and instructed to direct all study-related questions to the Helpline as the primary point of contact. The Helpline will triage calls directly to investigators and site staff, as appropriate.

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