Rationale and design of the Affordability and Real-world Antiplatelet Treatment Effectiveness after Myocardial Infarction Study (ARTEMIS): A multicenter, cluster-randomized trial of $P2Y_{12}$ receptor inhibitor copayment reduction after myocardial infarction

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Background The use of oral $P2Y_{12}$ receptor inhibitors after acute myocardial infarction (MI) can reduce risks of subsequent major adverse cardiovascular events (composite of all-cause death, recurrent MI, and stroke), yet medication persistence is suboptimal. Although copayment cost has been implicated as a factor influencing medication persistence, it remains unclear whether reducing or eliminating these costs can improve medication persistence and/or downstream clinical outcomes.

Design ARTEMIS is a multicenter, cluster-randomized clinical trial designed to examine whether eliminating patient copayment for $P2Y_{12}$ receptor inhibitor therapy affects medication persistence and clinical outcomes. We will enroll approximately 11,000 patients hospitalized for acute ST-elevation and non–ST-elevation MI at 300 hospitals. Choice and duration of treatment with a $P2Y_{12}$ receptor inhibitor will be determined by the treating physician. Hospitals randomized to the copayment intervention will provide vouchers to cover patients' copayments for their $P2Y_{12}$ receptor inhibitor for up to 1 year after discharge. The coprimary end points are 1-year $P2Y_{12}$ receptor inhibitor persistence and major adverse cardiovascular events. Secondary end points include choice of $P2Y_{12}$ receptor inhibitor, patient-reported outcomes, and postdischarge cost of care.

Conclusion ARTEMIS will be the largest randomized assessment of a medication copayment reduction intervention on medication persistence, clinical outcomes, treatment selection, and cost of care after acute MI. (Am Heart J 2016;177:33-41.)

Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor has become the cornerstone of antithrombotic therapy for secondary prevention after acute myocardial infarction (MI). The American Heart Association/American College of Cardiology guidelines for the management of ST-segment elevation MI (STEMI)[1] and non–ST-segment elevation acute coronary syndrome have recommended treatment for at least 1 year with $P2Y_{12}$ receptor inhibitors such as clopidogrel, ticagrelor, or prasugrel for percutaneous coronary intervention (PCI)–treated patients. However, recent studies have demonstrated that prasugrel and ticagrelor (which are the more potent $P2Y_{12}$ receptor inhibitors) are superior to clopidogrel in their ability to reduce major adverse cardiovascular events (MACEs), including death, MI, and stroke.[2,3] As a result, the 2014 non–ST-segment elevation acute coronary syndrome guidelines provide a IIa recommendation for ticagrelor in preference to clopidogrel in patients undergoing either an early invasive or ischemia-guided strategy, and for prasugrel in patients undergoing PCI.[4] European guidelines recommend ticagrelor as first-line therapy regardless of management strategy, prasugrel as

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first-line therapy for PCI-treated patients, and clopidogrel should be considered only if these agents are not available or are contraindicated.[5,6] Despite these recommendations, clopidogrel remains the dominant $P2Y_{12}$ receptor inhibitor used in the United States.[7-9]

Regardless of which $P2Y_{12}$ receptor inhibitor is initiated, medication adherence is suboptimal, with up to 60% of patients discontinuing therapy in the first year of treatment.[10,11] Such early drug discontinuation has been associated with worse clinical outcomes.[12-15] The cost of medications is often proposed as a major factor influencing both clinicians' drug choice and patients' long-term adherence to therapy.[16-19] 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.[20,16,21,22] Lower-income and older patients are at greater risk for cost-related medication nonadherence.[23,24] Health plan changes that move brand medications to a lower copayment tier have been associated with improved adherence.[25]

Clopidogrel is currently available in generic form, whereas ticagrelor and prasugrel are both currently only available as branded medications. Because most health plans have tiered prescription drug plans to provide incentives to use lower-cost medications, patient copayment for clopidogrel is often much less than that for the branded alternatives. This difference in patient copayment may influence both clinician $P2Y_{12}$ receptor inhibitor choice, as well as patient long-term persistence.

The Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) study was the first major randomized study to examine the effect of copay reduction on patient adherence. The study randomized post-MI patients to either usual prescription coverage or coverage for all prescription costs. Rates of adherence to secondary prevention medications were only 4% to 6% higher among the full-coverage group.[26] There was no significant reduction in the primary clinical outcome of first major vascular event or revascularization, but the prespecified secondary outcome of total major vascular events or revascularization was significantly lower among the full-coverage group, without a significant increase in total health care spending.[27] This study may have underestimated the potential impact of copayment reduction, because in many cases, the drugs that were evaluated were already associated with low copayments. Furthermore, there was a median delay of 49 days after discharge before drug coverage began, thereby missing the period when many patients self-discontinue medications, yet are at the highest risk for recurrent events. No other randomized trials have investigated the impact of copayment reduction on clinical end points among patients with MI. In addition, a copayment reduction strategy including both generic and branded medications has not been tested.

Table I. Patient inclusion and exclusion criteria

Inclusion criteria
Age ≥18 y
Hospitalized with STEMI or NSTEMI (see Table II for definitions)
Treated with a $P2Y_{12}$ receptor inhibitor at the time of enrollment
United States–based health insurance coverage with a prescription drug benefit
Have been fully informed and able to provide written consent for longitudinal follow-up
Exclusion criteria
History of intracranial hemorrhage
Contraindication to $P2Y_{12}$ receptor inhibitor at discharge
Involvement in another study that specifies the type or duration of $P2Y_{12}$ receptor inhibitor use within the next 12 mo
Life expectancy ≤1 y
Plans to move outside the United States within 1 y

These concepts formed the basis for the design of the ARTEMIS (ClinicalTrials.gov No. NCT02406677).

Methods

Design and study objectives

ARTEMIS is a large, practical, multicenter, cluster-randomized clinical trial that will assess whether reducing copayment for both a generic (clopidogrel) and brand (ticagrelor) $P2Y_{12}$ receptor inhibitor will increase long-term persistence of therapy and reduce risk of MACE at 1 year post-MI hospital discharge. ARTEMIS will also assess the impact of copayment reduction on $P2Y_{12}$ receptor inhibitor selection and use patterns, as well as total health care costs up to 1 year post-MI.

Site selection and study population

ARTEMIS will recruit approximately 300 US hospitals, enrolling approximately 11,000 patients with STEMI or non-STEMI (NSTEMI). To be eligible, hospitals must treat at least 50 MI patients annually and have both clopidogrel and ticagrelor available for clinical use on their hospital formulary. Patient inclusion and exclusion criteria are listed in Table I. Only patients providing informed consent for enrollment in the study will be included in study analyses.

Randomization and study intervention

After institutional review board approval, sites will be randomized in a 1:1 ratio to the copayment reduction intervention or usual care. Site randomization will be stratified by annual site MI volume and the baseline proportion of ticagrelor use at each site using permuted blocks.

$P2Y_{12}$ receptor inhibitor selection and treatment duration will be at the discretion of the patient's health care provider in accordance with local standards of care and practice. The ARTEMIS study protocol provides no recommendations directing treatment, and enrolled patients can be treated with any approved $P2Y_{12}$ receptor

inhibitor (ticlopidine, clopidogrel, prasugrel, or ticagrelor). For hospitals randomized to the copayment intervention arm, each study patient will be provided a voucher card at study enrollment. From the patient perspective, this voucher card can be used at any pharmacy to offset the patient copayment when filling all prescriptions for either clopidogrel or ticagrelor during the first 12 months post-MI. Medication refills need to be initiated by the patient at his/her pharmacy as in routine clinical care. For both local and mail-order pharmacies, when a patient initiates prescription filling, the patient copayment cost will be met by the study instead of the patient. For Medicare/Medicaid-insured patients who cannot receive copayment assistance, the voucher card will still offset copayments from the patient's perspective, but on the pharmacy end, the voucher card actually offsets the entire prescription cost of clopidogrel or ticagrelor. If a patient loses prescription drug coverage during the follow-up period, then the voucher card can be used to cover the entire cost of clopidogrel or ticagrelor for up to 1 year. Patients will be notified prior to 1 year after discharge to allow planning for continued dual antiplatelet therapy without the voucher copayment coverage, if recommended by the care provider. Among hospitals randomized to the control arm, all patients will receive usual care, and no study intervention will be performed. Patients treated with prasugrel or ticlopidine will not receive a study copayment voucher in either the control or intervention arm. If ARTEMIS only enrolled patients treated with clopidogrel or ticagrelor, trial participation itself may incentivize a bias in treatment selection. Thus, ARTEMIS enrollment is open to all eligible MI patients, and clinicians within both arms of the study are free to prescribe any P2Y12 inhibitor, including prasugrel or ticlopidine, for any enrolled patient.

End points

The coprimary end points are as follows: (1) MACE through 1 year after discharge and (2) persistence of $P2Y_{12}$ receptor inhibitor therapy at 1 year. Secondary end points include the following: (1) $P2Y_{12}$ receptor inhibitor type prescribed at index MI discharge and (2) total cost of health care between discharge and 1 year.

Clinical events

Major adverse cardiovascular event is defined as the composite of all-cause death, MI, or stroke. Relevant hospital medical records will be obtained and independently adjudicated by physicians at the Duke Clinical Research Institute (DCRI; Durham, NC) to ascertain each end point, using protocol-defined criteria (Table II). Other clinical events of interest include unplanned revascularization and bleeding. For bleeding, the Bleeding Academic Research Consortium and Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries definitions will be used. All study end points will be analyzed at 1 year after discharge, and an additional follow-up interview at 15 months will assess for changes in persistence or MACE after discontinuation of the copayment intervention.

Persistence

Persistence of $P2Y_{12}$ receptor inhibitor therapy is primarily defined as the continued use of any $P2Y_{12}$ receptor inhibitor between discharge and 1 year post-MI without a gap in treatment of more than 30 days, as reported by the patient. Patient-reported persistence will be validated in a subset of patients using 2 methods: prescription fills from pharmacy records and plasma drug/metabolite levels. First, from pharmacy records, prescription fills covering the time since discharge without gap in treatment more than 30 days will be considered persistent. Pharmacy records will also be used to calculate patient adherence, defined as the proportion of days covered by prescription fills. Second, 1000 randomly selected patients (500 in each arm) will provide blood samples at one of the follow-up time points: 3, 6, 9, or 12 months. Drug or metabolite levels of clopidogrel, ticagrelor, and prasugrel will be measured. Detection of drug or drug metabolite in blood samples within 24 hours of last ingested dose will be considered persistent.

Health care costs

Health care costs will be collected for each emergency department visit, rehospitalization, or hospital-based procedure. Two major types of medical costs will be assessed: (1) hospital costs (including emergency department costs unassociated with hospital admission) and (2) physician service costs. To perform a charge-to-cost conversion, 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.[28] Copayment costs covered by the study voucher among subjects in the intervention arm will be collected.

Data collection

Details of the index hospitalization will be collected by participating sites for each enrolled patient via an electronic data collection tool. Baseline data will include sociodemographic information, medical history and comorbidities, presentation characteristics, in-hospital and discharge medications, angiographic and procedural

Table II. Event definitions

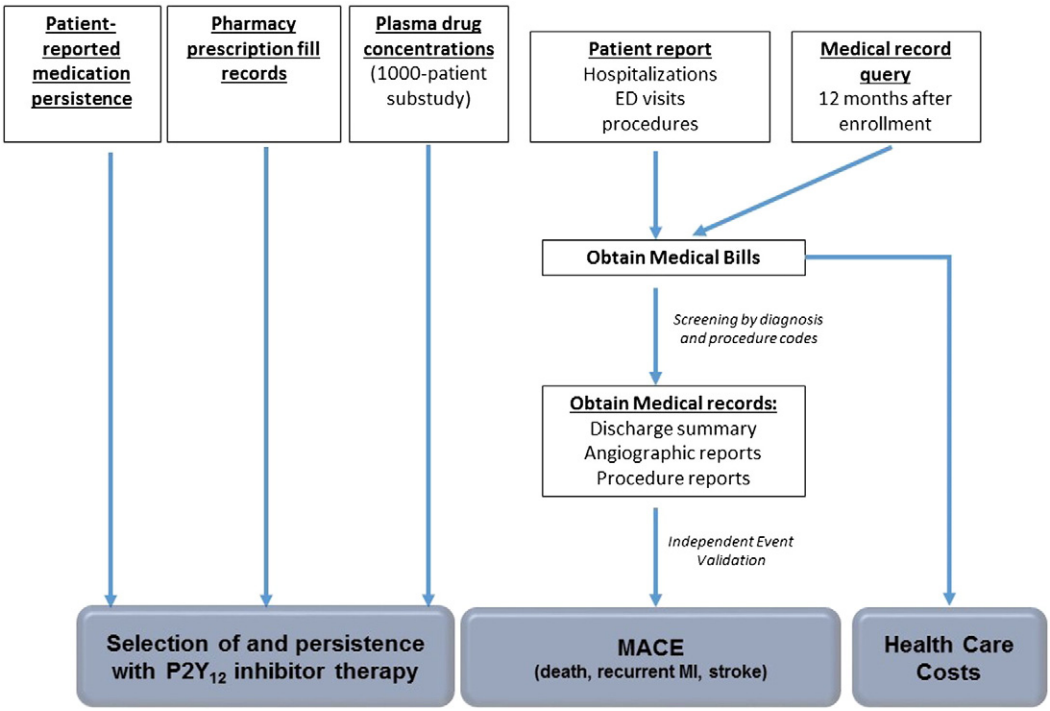
MACE	Composite of all-cause death, MI, or stroke
All-cause death	Death due to any reason
Cardiovascular death	Death due to any of the following: 1. Any mechanism (arrhythmia, heart failure, shock) related to and within 30 days after an MI, including death resulting from a procedure 2. Sudden cardiac death 3. Heart failure or cardiogenic shock 4. Stroke 5. Other cardiovascular causes (dysrhythmia, pulmonary embolism, cardiovascular intervention, etc)
MI	A rise and fall of cardiac biomarkers with at least 1 value above the institutional ULN associated with at least one of the following: 1. Symptoms of ischemia 2. New (or presumed new) ST-segment or R-wave changes, or LBBB 3. Development of pathologic Q-waves on the ECG 4. Imaging evidence of new loss of myocardium or new wall motion abnormality 5. Identification of intracoronary thrombus by angiography or autopsy
Stroke	Loss of neurologic function caused by an ischemic or hemorrhagic event with residual symptoms at least 24 h after onset or leading to death
BARC bleeding	Type 1: Bleeding that is not actionable and does not cause the subject to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional Type 2: Any overt, actionable sign of hemorrhage that does not fit the criteria for type 3, 4, or 5, but does meet at least one of the following criteria: (1) requiring nonsurgical and medical intervention, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation Type 3a: Overt bleeding plus hemoglobin drop of 3 to <5 g/dL or any transfusion Type 3b: Overt bleeding plus hemoglobin drop of ≥5 g/dL or cardiac tamponade or requiring surgical intervention or requiring intravenous vasoactive agents Type 3c: Intracranial hemorrhage or intraocular bleed compromising vision Type 4: CABG-related bleeding Type 5: Fatal bleeding
GUSTO bleeding	Mild: Bleeding that does not meet the criteria for either severe or moderate bleeding Moderate: Bleeding that requires transfusion, but does not result in hemodynamic compromise Severe or life-threatening: Intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention
Unplanned coronary revascularization	Any unplanned revascularization of >1 coronary vessels occurring after the index hospitalization. Staged coronary revascularizations that are planned at the time of the index procedure and completed within 60 d will not be considered an unplanned revascularization event, unless there is a documented recurrent ischemic episode determining the timing of the procedure.

Abbreviations: *BARC*, Bleeding Academic Research Consortium; *CABG*, coronary artery bypass grafting; *ECG*, electrocardiogram; *GUSTO*, Global Utilization of Streptokinase and t-PA for Occluded Arteries; *LBBB*, left bundle-branch block; *ULN*, upper limit of normal.

characteristics, in-hospital events, and medications prescribed at discharge (including $P2Y_{12}$ receptor inhibitor type). In addition, patients will complete a survey including measures addressing: health literacy, access to medical care, medication-taking behaviors, financial burden of medications, depression, general health status, disease impact, angina frequency, and preferences for medication use. Follow-up questionnaires at 3, 6, 9, and 12 months will also selectively collect patient-reported measures. These measures will assist in our understanding of long-term medication persistence behavior.

After discharge, longitudinal information will be collected during the follow-up stage on patient treatment ($P2Y_{12}$ receptor inhibitor use and concomitant medications), effectiveness and safety outcomes, and resource use. Follow-up will occur every 3 months after discharge up to 15 months via a centralized telephone interview conducted by trained personnel at the DCRI or a Web-based survey, based on patient preference and feasibility. If Web-based data collection is incomplete, then the DCRI will follow up via telephone to minimize missing data. At each interview, patients will be asked to report current medications, interval rehospitalizations,

Figure



Data collection and event assessment. This figure displays a flowchart of how the data will be collected, as well as how events will be validated. ED, emergency department.

and health status. Temporary discontinuation and switching of $P2Y_{12}$ receptor inhibitor types will be assessed at each follow-up interview.

Based on patient-reported events, medical billing data for any hospitalization, emergency department visit, or procedure will be obtained.[29] If a MACE or bleeding event is suspected on the basis of a billed diagnosis code or procedure, additional relevant clinical documentation will be collected and independently reviewed by a study physician at the DCRI to validate patient-reported events. Physicians performing event validations will be blinded to the randomized assignment of the participating hospitals (copayment reduction vs usual care). As an additional mechanism to safeguard against event underreporting or loss to follow-up, sites will conduct a medical record query 1 year after the last enrolled patient to screen for any hospitalizations or procedures (Figure).

Statistical considerations

The proposed sample size was selected to provide adequate statistical power for the coprimary study objectives. For the 1-year MACE end point, we assume a control group event rate of 12%. To achieve 80% power to detect an 18% relative reduction in the primary end point (which was considered clinically meaningful) with a patient-level randomization, a 1:1 allocation ratio, and a 2-sided type I error rate of 0.05 would require a total of 6,728 patients. Under the same assumptions, a total sample size of 7,670 would provide 85% power. However, given that the sample size needs to be adjusted due to the cluster-randomized design, we applied the method described by Eldridge et al[30] to account for the coefficient of variation (CV) of cluster size and the intracluster correlation (ICC). A prior multicenter study suggested an ICC of approximately 0.01 for the MACE end point. The CV of 0.65 has been suggested by others and can be guided by providing minimum and maximum enrollment at the site level. 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 7,278 patients. 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%).

For the $P2Y_{12}$ receptor inhibitor persistence end point, an increase of 4% would be considered a clinically important difference.[26] To achieve this objective with a patient-level randomization design and assuming 1-year persistence of 70% in the usual-care group, a sample size of 5,392 patients would provide greater than 90% power

with a 2-sided type I error rate of 0.05. A sample size of 4,622 patients would provide greater than 85% power under the same assumptions. To account for the cluster-randomized design, we anticipate an ICC for this end point of approximately 0.025 based on a prior multicenter trial. Assuming a total of 300 sites 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 (ie, 11,000/2.28) and be sufficient to provide between 85% and 90% power to detect an absolute 4% difference between treatment groups in the cluster-randomized design.

As a cluster-randomized trial, all outcomes will be compared between eligible and consented MI patients receiving care in hospitals randomized to the copayment intervention and those patients receiving care in hospitals randomized to usual care. Outcomes are compared regardless of whether the patient used the study voucher. Separate analyses will be conducted for all consented patients discharged on clopidogrel or ticagrelor, and repeated for all consented patients regardless of discharge P2Y12 receptor inhibitor type. Cox proportional hazard modeling will be applied to assess differences in the time to first MACE event up to 1 year after hospital discharge between groups after adjustment for patient demographic and baseline clinical characteristics. Events will be censored at the time of discontinuation from the study due to loss to follow-up or withdrawal. To compare the rate of persistence between intervention and control arms, multivariable logistic regression and Cox proportional hazards models with adjustment for differences in patient characteristics between groups will be conducted. General estimating equations will be applied to examine the impact of correlated responses within enrolling hospitals. Analyses of medication persistence and MACE will be examined among those discharged on $P2Y_{12}$ receptor inhibitor options for which study vouchers are provided (clopidogrel or ticagrelor), as well as in the overall population regardless of $P2Y_{12}$ receptor inhibitor type.

An interim assessment will be conducted at 1 year after initiation of enrollment to review the overall MACE event rate and determine the need for adjustment of the enrollment target. No interim analyses of outcomes for the purpose of stopping the study prior to completion of enrollment are planned.

Ethical considerations

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. The Duke University Medical Center Institutional Review Board approved the study, and the study will be submitted to local or central institutional review boards for approval whenever required by local institutional guidelines. All patients will provide individual informed consent for study participation and authorization for the use and disclosure of their personal health information. De-identified data will be used for data analysis, and the confidential nature of patient information will be maintained.

The ARTEMIS trial is led by a Steering Committee with a coordinating center at the DCRI. The study design reflects collaborative input provided by the Steering Committee composed of academic thought leaders, specialists in MI care, and health services researchers. The authors of this manuscript are solely responsible for the design and conduct of the study, and the drafting and editing of the manuscript and its final contents. The trial is sponsored by AstraZeneca.

Discussion

The ARTEMIS trial will be the largest randomized assessment of the impact of copayment reduction on medication use and clinical outcomes among patients with acute MI. The trial focuses on use of $P2Y_{12}$ receptor inhibitors after MI, but the results may be applicable to other medical conditions in which medication adherence is important in determining outcomes. Prior interventions for improving medication adherence have been complex and costly, and have shown marginal benefit when successful.[31,32] A copayment reduction strategy is attractive because it could be simply and broadly implemented, and would be complementary to other adherence promotion efforts. The MI FREEE study demonstrated that copayment elimination can produce significant improvement in adherence to traditional evidence-based post-MI medications (β-blockers, angiotensin-converting enzyme inhibitors, and statins).[26] ARTEMIS will determine if copayment reduction of an antiplatelet agent starting at the time of discharge can provide greater improvement in medication adherence and, ultimately, improve clinical outcomes.

We hypothesize that any reduction in MACE can be attributed to improved medication persistence due to lower out-of-pocket costs for the patient, irrespective of $P2Y_{12}$ receptor inhibitor type. In addition, by reducing out-of-pocket patient cost for both generic and nongeneric treatment options, we hypothesize that clinician choice of antiplatelet therapy will primarily be driven by risk-benefit assessment, rather than perceived patient affordability, leading to a change in prescribing patterns. This may lead to increased and more selective utilization of higher potency $P2Y_{12}$ receptor inhibitors shown to improve outcomes. The combination of more risk-driven clinical decision making with improved longitudinal medication persistence contributes to the clinical efficacy of this strategy. If there is evidence of improved clinical efficacy, then the reduction in MACE could provide

savings to offset the cost of the copayment intervention that incentivizes the use of branded medications. This is in contrast to the strategy of most pharmacy benefit plans that use tiered copayments to encourage prescription of the least expensive medication in a therapeutic class. Consequently, the results of ARTEMIS have the potential to drive patient-centered changes in medication coverage and cost-sharing strategies for insurers and health systems.

ARTEMIS has several notable design elements. First, cluster randomization will be used to assess the impact of the copayment intervention on both patient and hospital behavior. Whether a copayment intervention will change drug selection patterns by health care providers is unclear. A previous study that offered providers a no-cost diagnostic test appeared to increase test use, but adoption was not universal and rarely influenced medical decision-making.[33] By randomizing at the hospital level and preserving the provider's ability to choose treatment, cost to the patient is no longer a consideration; therefore, ARTEMIS will allow us to assess provider treatment decision making. Patient-level randomization would not permit assessment of provider practice pattern changes.

ARTEMIS will also use a novel centralized system for follow-up. Specifically, patient-reported events will be validated and supplemented with hospital bills and clinical documentation, which identifies patient overreporting and underreporting of events.[34] This method, successfully implemented in the Treatment with ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) registry with minimal loss to follow-up (3% at 1 year),[29] reduced the burden of follow-up for sites and patients in this pragmatic randomized trial. ARTEMIS takes this a step further by offering patients the option of either telephone or Web-based follow-up. If Web-based data collection is incomplete, then the DCRI will follow up via telephone to minimize missing data. The characterization of patients who prefer Web-based follow-up, as well as the quality of data collected from Web-based follow-up, will be of interest to those conducting future pragmatic trials.

Direct measurement of patient medication-taking behavior, such as pill counts, is not practical for a large clinical trial. In the ARTEMIS study, persistence with $P2Y_{12}$ receptor inhibitor therapy will be assessed in 3 different, albeit complementary, ways: (1) patient report, (2) pharmacy data, and (3) serum drug/metabolite levels. Each of these 3 methods has limitations. Patient report, although the least costly method, may overestimate persistence. A previous study using similar follow-up mechanisms and definition of persistence demonstrated reasonable estimates of persistence.[35] In the absence of a universal pharmacy record, collection of individual pharmacy fill records has been successfully implemented on a local scale,[36] but not nationally. Obtaining serum drug levels can be considered the "gold standard," as it directly confirms ingestion of the drug, but is more invasive and costly. In ARTEMIS, we will have the opportunity to compare $P2Y_{12}$ receptor inhibitor persistence using these 3 methods. Our results will provide guidance for the design of future studies assessing medication-taking behavior.

ARTEMIS will also gather comprehensive health care cost data, including the cost of medication copayments among the intervention arm. Copayment costs vary widely based on insurance plans and pharmacies in the United States. ARTEMIS provides a unique opportunity to examine copayment variability and the impact of out-of-pocket cost on medication-taking behavior. Finally, ARTEMIS will capture a variety of patient-centered variables to better characterize barriers to medication adherence. Clinical trials rarely obtain detailed patient-reported data on social support, financial burden, or preferences for treatment. The capture of these factors will help us interpret the overall results of the study and assist in our understanding of long-term medication persistence behavior.

Conclusion

There remains room for improvement in the long-term care and outcomes of patients with acute MI. The ARTEMIS trial is a large multicenter trial testing the impact of $P2Y_{12}$ receptor inhibitor copayment reduction on medication selection, long-term persistence, clinical outcomes, and cost of care. The trial will generate valuable evidence for clinical practitioners, patients, and policymakers.

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