ORIGINAL RESEARCH

Impact of a Copayment Reduction Intervention on Medication Persistence and Cardiovascular Events in Hospitals With and Without Prior Medication Financial Assistance Programs

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BACKGROUND: Hospitals commonly provide a short-term supply of free P2Y\textsubscript{12} inhibitors at discharge after myocardial infarction, but it is unclear if these programs improve medication persistence and outcomes. The ARTEMIS (Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) trial randomized hospitals to usual care versus waived P2Y\textsubscript{12} inhibitor copayment costs for 1-year post-myocardial infarction. Whether the impact of this intervention differed between hospitals with and without pre-existing medication assistance programs is unknown.

METHODS AND RESULTS: In this post hoc analysis of the ARTEMIS trial, we examined the associations of pre-study free medication programs and the randomized copayment voucher intervention with P2Y\textsubscript{12} inhibitor persistence (measured by pharmacy fills and patient report) and major adverse cardiovascular events using logistic regression models including a propensity score. Among 262 hospitals, 129 (49\%) offered pre-study free medication assistance. One-year P2Y\textsubscript{12} inhibitor persistence and major adverse cardiovascular events risks were similar between patients treated at hospitals with and without free medication programs (adjusted odds ratio 0.93, 95\% CI, 0.82–1.05 and hazard ratio 0.92, 95\% CI, 0.80–1.07, respectively). The randomized copayment voucher intervention improved persistence, assessed by pharmacy fills, in both hospitals with (53.6\% versus 44.0\%, adjusted odds ratio 1.45, 95\% CI, 1.20–1.75) and without (59.0\% versus 48.3\%, adjusted odds ratio 1.46, 95\% CI, 1.25–1.70) free medication programs ($P_{interaction}=0.71$). Differences in patient-reported persistence were not significant after adjustment.

CONCLUSIONS: While hospitals commonly report the ability to provide free short-term P2Y\textsubscript{12} inhibitors, we did not find association of this with medication persistence or major adverse cardiovascular events among patients with insurance coverage for prescription medication enrolled in the ARTEMIS trial. An intervention that provided copayment assistance vouchers for 1 year was successful in improving medication persistence in hospitals with and without pre-existing short-term medication programs.

REGISTRATION: URL: https://www.clinicaltrials.gov/. Unique identifier: NCT02406677.

Key Words: medication adherence • myocardial infarction • quality improvement

Medication non-adherence after myocardial infarction (MI) is common and is associated with adverse cardiovascular outcomes.\textsuperscript{1–4} Guidelines recommend P2Y\textsubscript{12} inhibitors for at least 1 year after an MI,\textsuperscript{5,6} but premature discontinuation of P2Y\textsubscript{12} inhibitors can lead to stent thrombosis and
CLINICAL PERSPECTIVE

What Is New?
- Hospitals frequently use medication assistance programs to reduce the cost of medications after myocardial infarction, but these programs were not associated with an improvement in P2Y_{12} inhibitor persistence, whereas the randomized copayment intervention tested in the ARTEMIS (Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) was associated with improved persistence.

What Are the Clinical Implications?
- Hospitals and payers may consider strategies that provide long-term reduction of copayments for critical secondary prevention medications, rather than short-term support at the time of discharge.

Nonstandard Abbreviations and Acronyms

| Acronym   | Description                                           |
|-----------|-------------------------------------------------------|
| ARTEMIS   | The Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study |
| MACE      | major adverse cardiovascular events                   |
| MI FREE   | The Post-Myocardial Infarction Free RX Event and Economic Evaluation Trial |

recurrent MI with often fatal outcomes.\(^7\,\^8\) Among hospitals in the United States, there is significant variability in medication adherence after MI, and patients discharged from hospitals with low adherence rates have higher incidence of major adverse cardiovascular events (MACE).\(^9\) In response to these concerns, hospitals have enacted varying strategies to promote optimal secondary prevention medication use. Many of these strategies have not been formally evaluated and, in those that have been, their effectiveness is mixed.\(^10\,\^12\) Medication cost is a common and significant barrier to adherence.\(^13\) For patients with financial barriers to medication adherence, some hospitals offer a free 30-day supply of medications at discharge to promote initial adherence and prevent rehospitalizations. The prevalence of use and potential impact of such free short-term medication programs on longitudinal medication persistence and patient outcomes are unknown.

The ARTEMIS (Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) trial randomized hospitals to usual care versus the ability to waive copayment out-of-pocket costs for P2Y_{12} inhibitor fills for 1 year.\(^14\) The intervention enhanced guideline-adherent P2Y_{12} inhibitor selection and longitudinal medication persistence, but did not significantly reduce MACE.\(^15\) Participating hospitals were surveyed on strategies used to promote optimal medication use before and after ARTEMIS study participation, including whether hospitals had the ability to provide a free 30-day supply of a P2Y_{12} inhibitor to patients at MI discharge. We hypothesized that patients treated at hospitals with pre-existing free medication programs would already have better medication persistence and outcomes compared with those treated at hospitals without pre-existing free medication programs. Thus, these hospitals would less likely benefit from the randomized ARTEMIS copayment intervention than hospitals without pre-existing free medication programs.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subjects confidentiality protocols may be sent to the Duke Clinical Research Institute at tracy.wang@duke.edu. The ARTEMIS trial was a cluster-randomized trial assessing the impact of a copayment reduction intervention on 1-year P2Y_{12} inhibitor persistence and MACE in patients hospitalized for acute MI. The design of ARTEMIS has been previously reported in detail.\(^14\,\^15\) In brief, hospitals were eligible for randomization if they treated at least 50 MI patients annually and had both clopidogrel and ticagrelor available for clinical use. In both randomized hospital groups, enrolled patients were aged >18 years, hospitalized for MI, treated with a P2Y_{12} inhibitor during the hospitalization, and had any US-based health insurance with a prescription drug plan. Overall, 26 006 patients were screened for the ARTEMIS study, and enrollment rates were higher at intervention hospitals (6436 of 18 803 screened patients, 34%) than control hospitals (4565 of 20 436 screened patients, 22.3%). Of 11 001 patients enrolled from 287 hospitals between June 6, 2015 and September 20, 2016, we excluded patients who died during the index admission or withdrew from the study before discharge (n=25), were not discharged on clopidogrel or ticagrelor (n=874), or were treated at sites that did not complete the pre-enrollment hospital survey questions (n=512 patients at 25 sites). Our final study population included 9590 patients from 262 hospitals (Figure 1). The study was
approved by the institutional review boards at Duke University and all participating sites. All patients provided written informed consent for participation in the ARTEMIS study.

Sites randomized to the copayment intervention provided subjects with a voucher that allowed them to fill clopidogrel or ticagrelor at any pharmacy without out-of-pocket copayment costs for 1-year post-MI. Decisions on P2Y12 inhibitor drug choice and treatment duration were left to the treating clinician. The protocol did not prohibit the use of any other strategies to optimize medication use; sites in either arm could continue pre-existing programs, or initiate new interventions, during participation in ARTEMIS. We therefore performed a post hoc, non-prespecified analysis of the ARTEMIS study to assess associations of pre-existing assistance programs with medication persistence and outcomes.

Before randomization and patient enrollment, each site completed a survey of their hospital’s practices related to transition of care and medication persistence promotion; the survey was completed by a clinician involved in the discharge of patients with MI at that hospital who was familiar with institutional discharge practices. The site survey included a question: “Does your hospital provide medication assistance to patients who cannot afford the prescribed P2Y12 inhibitor therapy?” Hospitals that answered “we provide drug for a short period (30 days) sponsored by the hospital,” or “we provide drug for a short period sponsored by someone else (eg, pharmaceutical company samples)” were defined as hospitals offering free short-term medication assistance before ARTEMIS study participation. All other responses (“provide discount vouchers,” “apply on patient’s behalf for prescription assistance programs,”

Figure 1. Study population.
ARTEMIS indicates Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study trial.
“refer patient to pharmacies/clinics that have prescription assistance, discount generic programs, or samples,” “provide other medication assistance,” or “no assistance provided”) did not provide patients with a free short-term supply of medication, therefore these hospitals were not defined as providing free medication assistance. Additional questions focused on other medication use optimization strategies, discharge practices, and hospital quality improvement systems. One year after the site completed study enrollment, 210 sites (80%) completed a follow-up survey that included the same question.

P2Y12 inhibitor persistence, measured by patient report, and MACE were co-primary end points of the ARTEMIS study. As patient report overestimates medication persistence, persistence was also defined as no gap in P2Y12 inhibitor supply >30 days using pharmacy fill data from Symphony Health Solutions, which captures pharmacy claims data from ≈90% of retail, 60% of mail-order, and 70% of specialty pharmacies in the United States.17 Pharmacy fill data were available for 7942 patients (82.8%). Persistence was measured at 90-days and 1-year post-MI. For patients who died or had missing persistence data before 1 year, the last observation carried forward method was used for persistence up to 1 year. MACE was defined as the composite of all-cause death, MI, or stroke within 1-year post-MI. Events were independently adjudicated by physicians at the coordinating center as previously described.14

All patients completed a survey at enrollment which included items related to medication-taking behavior and financial burden. Missingness rates were low (<4%) for all of these items. We compared characteristics of hospitals with and without pre-study free short-term medication programs, and well as the demographic, clinical, and treatment characteristics of patients treated at these hospitals. Categorical variables were presented as frequencies and differences between groups were assessed using Chi-square test or an exact test as appropriate. Continuous variables were presented as median (interquartile range) and compared using the Wilcoxon rank-sum test.

We compared outcomes of patients treated at hospitals with and without pre-study free short-term medication programs. P2Y12 inhibitor persistence comparisons were adjusted for patient and hospital characteristics using logistic regression models with parameters estimated using generalized estimating equations to account for within-hospital clustering. MACE outcomes were compared using Cox regression models with adjustment for patient and hospital characteristics and robust standard errors to account for within-hospital clustering. Covariates included age, sex, race, insurance payor, region, pre-enrollment site MI volume and proportion of ticagrelor use, an indicator for randomization scheme (2:1 versus 1:1), an indicator variable for randomization status (intervention versus control), as well as a propensity score that estimated likelihood of treatment at a hospital with pre-study free medication programs using a logistic regression model containing 51 covariates selected a priori based on clinical relevance (Table S1, Figure S1). All covariates were included in the model regardless of whether there were statistically significant differences between groups. In a sensitivity analysis, we assessed the association of free medication programs with outcomes among hospitals randomized to the copayment voucher intervention or usual care by developing separate logistic regression models for each group.

We then assessed the impact of the randomized intervention on persistence and MACE among hospitals with and without pre-study free medication programs using similar methodology, though a separate propensity score was developed for the likelihood of assignment to the intervention group (versus control) (Table S1, Figure S2). We then tested the interaction of pre-study free medication programs and randomization groups with regard to persistence and MACE. Among hospitals randomized to the intervention, we assessed for any imbalance in use of the copayment waiving voucher between patients treated at hospitals with and without pre-study free medication programs.

One year after sites completed study enrollment, sites completed a follow-up survey that again asked: “Does your hospital provide medication assistance to patients who cannot afford the prescribed P2Y12 inhibitor therapy?” We calculated the proportion of sites now defined as providing free short-term medication assistance. Among sites that did not offer pre-study free medications, we calculated the proportion of sites that converted to providing free short-term medication assistance.

Missingness was <1% for all clinical variables, <5% for all patient-reported variables, and <10% for all hospital survey questions. We imputed missing medical history, home medications, admission features, and in-hospital events to the mode. Socioeconomic variables, laboratory values, and weight were imputed to age-, sex-, and race-specific modes for categorical variables and medians for continuous variables. A \( P \leq 0.05 \) was considered statistically significant for all tests. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc).

RESULTS
Among 262 hospitals participating in the ARTEMIS trial, 49% (n=129 centers enrolling 5051 patients) reported pre-study free short-term medication assistance (ie,
the ability to provide patients with a free 30-day supply of P2Y$_{12}$ inhibitors at discharge. These included 29 hospitals (11.1%) that covered the cost of the drug directly, 81 (30.9%) that provided drug that was sponsored by a pharmaceutical company, and 19 (7.3%) that had both options available.

Hospitals with and without free medication programs had no significant differences in size, teaching status, geographic distribution, and profit status, however hospitals with free short-term medication programs more often included a case manager or care coordinator in the discharge process and filled outpatient P2Y$_{12}$ inhibitor prescriptions before the patient left the hospital; alternative medication cost reduction strategies, such as the provision of commercial discount vouchers, were also used more frequently at these hospitals (Table 1). Several non-financial strategies were commonly used by hospitals with and without pre-study free medication programs, including: a discharge medication list providing rationale for each medication, phone contact within 1 week of discharge, and a 24-hour call center for patient concerns (Table 1).

Patients enrolled at free medication hospitals were more likely to be of white race and present with non-ST-segment-elevation myocardial infarction, and to be treated with ticagrelor during hospital admission and at time of discharge (Table 2). Overall, half of the patients reported financial hardship related to filling prescription medications, 17% had not filled a prescription because of cost within the prior 3 months, and cost was frequently ranked as an “extremely important” factor in medication decision-making (Figure 2). Compared with patients treated at hospitals without free medication programs, patients treated at hospitals with free medication programs more often considered cost “extremely important” (49% versus 45%, P<0.01) and reported financial hardship (51% versus 49%, P<0.05).

Overall, persistence to P2Y$_{12}$ inhibitors was 96% at 90 days and 86% at 1 year when assessed by patient report. Persistence assessed by pharmacy fills was 72% at 90 days and 52% at 1 year. Pre-study free short-term medication programs were not associated with differences in short- or long-term medication persistence rates or MACE in either unadjusted or adjusted analyses (Table 3, Figure S3). Outcomes of patients treated at hospitals with pre-study free medication programs were not significantly different from those treated at hospitals without free medication programs, when examined separately by randomized arm (Tables S2 and S3).

However, the randomized copayment intervention led to increased 1-year medication persistence, in both hospitals with and without pre-existing medication assistance programs (Table 4). This effect persisted after multivariable adjustment for pharmacy-based

Table 1. Site Characteristics and Adherence Promotion Strategies at Hospitals With and Without Pre-Study Free Medication Programs

| Variable | Free Medication Program | No Free Medication Program | P Value |
|----------|-------------------------|----------------------------|---------|
| n        | 129                     | 133                        |         |
| Site characteristics | | | |
| Total hospital beds, median (IQR) | 381 (276, 601) | 393 (270, 555) | 0.66 |
| Teaching hospital | 29% | 24% | 0.40 |
| Profit status | | | 0.27 |
| Not-for-profit | 81% | 73% | |
| For-profit | 9% | 14% | |
| Government | 11% | 13% | |
| Region | | | 0.92 |
| Northeast | 18% | 20% | |
| Midwest | 33% | 29% | |
| South | 38% | 40% | |
| West | 12% | 12% | |
| Medication use optimization strategies | | | |
| Routine participation in patient discharge† | | | |
| Pharmacist | 38% | 32% | 0.28 |
| Care coordinator/case manager | 84% | 57% | <0.01 |
| Social worker | 45% | 37% | 0.18 |
| Dedicated transition of care nurse | 32% | 36% | 0.51 |
| Routinely screens patients for* | | | |
| Medication non-adherence | 48% | 42% | 0.35 |
| Ability to afford medications | 75% | 65% | 0.08 |
| Call pharmacy to check P2Y$_{12}$ inhibitor cost | 17% | 23% | 0.22 |
| Provides commercial discount vouchers for P2Y$_{12}$ inhibitor‡ | 66% | 53% | 0.03 |
| Apply for P2Y$_{12}$ inhibitor prescription assistance on patient’s behalf§ | 40% | 30% | 0.08 |
| On-site pharmacy fills P2Y$_{12}$ inhibitor before patient leaves the hospital¶ | 33% | 17% | <0.01 |
| Discharge medication list describing rationale for each medication* | 84% | 72% | 0.05 |
| Phone contact within 1 wk of discharge* | 65% | 51% | 0.02 |
| 24-h call center for patient concerns* | 57% | 52% | 0.44 |

IQR indicates interquartile range.

†Hospital performs this for >50% of all myocardial infarction patients before hospital discharge.

‡Discount vouchers include coupons distributed by pharmaceutical manufacturers, prescription benefit managers, pharmacies, or marketing companies.

§Prescription assistance programs are generally funded by pharmaceutical companies to provide lower cost medications to applicants that demonstrate financial need.
The intervention did not lead to a significant change in MACE in either hospital group. Among hospitals randomized to the copayment voucher intervention, all patients received a copayment waiving voucher at discharge, and voucher usage rates over the next year were similar at hospitals with and without pre-study free medication programs (73.2% versus 71.9%, \( P = 0.29 \)).

At 1 year after completing study enrollment, 210/262 (80.2%) hospitals completed a follow-up survey. More hospitals (59.5%, \( n = 125 \)) now reported ability to provide short-term free P2Y\textsubscript{12} inhibitor at discharge. Among hospitals completing the follow-up survey without free medication programs at baseline, 53/107 (49.5%) converted to providing free medication programs; this was not significantly different between sites randomized to the copayment intervention versus usual care (43.5% versus 54.1%, \( P = 0.28 \)).

DISCUSSION

Before participation in the ARTEMIS trial, approximately half of hospitals already offered a free short-term supply of P2Y\textsubscript{12} inhibitors to patients who cannot afford treatment. However, patients treated at these hospitals did not have better 1-year medication persistence or MACE rates compared with patients treated at hospitals that did not offer this type of short-term medication assistance. In contrast, we found that the ARTEMIS intervention—waived P2Y\textsubscript{12} inhibitors copayments for the guideline-recommended 1-year course—was associated with improved persistence, and this effect was similar in both hospitals with and without pre-existing free short-term medication programs. This suggests that longer-term financial assistance strategies may be more effective than short-term support in improving patient persistence to medications.

Hospitals used varying strategies to promote medication persistence after discharge. In our survey, many hospitals invest resources in screening for potential non-adherence, providing medication reminder tools and/or pharmacist-led education. In

### Table 2. Characteristics of Patients Admitted With Myocardial Infarction to Sites With and Without Pre-Existing Free Medication Programs

| Variable                              | Free Medication Program | No Free Medication Program | \( P \) Value |
|---------------------------------------|-------------------------|----------------------------|--------------|
| n                                     | 5051                    | 4539                       |              |

**Patient demographics**

| Age, y, median (IQR) | 62 (54–70) | 62 (54–70) | 0.55 |
|----------------------|------------|------------|------|
| Men                  | 69%        | 67%        | 0.26 |
| Race                 |            |            |      |
| White                | 89%        | 87%        | <0.01|
| Black                | 9%         | 11%        | <0.01|
| Other                | 3%         | 3%         | 0.86 |

**Insurance payer**

| Private | 63% | 64% | 0.41 |
|---------|-----|-----|------|
| Medicare| 43% | 43% | 0.67 |
| Medicaid| 9%  | 9%  | 0.43 |
| Other   | 10% | 8%  | 0.04 |

**Medical history**

| Hypertension | 69% | 69% | 0.57 |
|--------------|-----|-----|------|
| Diabetes mellitus | 33% | 32% | 0.59 |
| Dyslipidemia  | 58% | 59% | 0.64 |
| Dialysis      | 2%  | 2%  | 0.65 |
| Prior MI      | 21% | 20% | 0.19 |
| Prior PCI     | 26% | 25% | 0.16 |
| Prior CABG    | 11% | 11% | 0.23 |
| Prior TIA/stroke | 7%  | 7%  | 0.40 |
| Prior heart failure | 7%  | 8%  | 0.15 |
| Current/recent smoker | 35% | 32% | 0.02 |

**Presentation and treatment**

| STEMI | 45% | 47% | 0.02 |
|-------|-----|-----|------|
| Cardiogenic shock | 2%  | 3%  | 0.27 |
| Cardiac arrest     | 3%  | 3%  | 0.72 |
| Diagnostic angiography | 98% | 98% | 0.07 |
| PCI              | 88% | 90% | 0.08 |
| CABG             | 1%  | 2%  | 0.06 |

**P2Y\textsubscript{12} inhibitor use**

| Home P2Y\textsubscript{12} inhibitor use | 14% | 15% | 0.39 |
|-----------------------------------------|-----|-----|------|

**In-hospital**

| Clopidogrel | 48% | 57% | <0.01 |
|-------------|-----|-----|------|
| Ticagrelor  | 62% | 55% | <0.01 |

**At discharge**

| Clopidogrel | 43% | 52% | <0.01 |
|-------------|-----|-----|------|
| Ticagrelor  | 57% | 48% | <0.01 |

**Patient survey responses**

| Medication cost is extremely important | 49% | 45% | <0.01 |

(Continued)
Doll et al. Medication Assistance Programs After MI

In the last 3 months, have you decided not to fill a prescription medication because it was too expensive?

Table 3. The Association of Hospital Use of Pre-Study Free Medication Programs (Vs No Free Medication Programs) With P2Y12 Inhibitor Persistence and MACE

| Outcome              | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|----------------------|------------------------|----------------------|
| 90-d persistence     |                        |                      |
| Patient report       | 1.18 (0.92–1.51)        | 1.11 (0.89–1.40)     |
| Pharmacy fill        | 1.01 (0.86–1.19)        | 0.98 (0.83–1.15)     |
| 1-y persistence      |                        |                      |
| Patient report       | 1.03 (0.87–1.22)        | 1.01 (0.86–1.18)     |
| Pharmacy fill        | 0.95 (0.83–1.10)        | 0.93 (0.82–1.05)     |
| 1-y MACE             | 0.95 (0.78–1.15)        | 0.92 (0.80–1.07)     |

HR indicates hazard ratio; MACE, major adverse cardiovascular events; and OR, odds ratio.

Figure 2. Responses to the baseline patient survey on medication cost and cost-related non-adherence, administered to all subjects at time of enrollment in ARTEMIS (The Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) (n=9590).

particular, interventions addressing financial barriers to medication use are common; these include dedicated resources to assess drug affordability, troubleshoot financial barriers, and facilitate medication filling. Many hospitals in our study have taken on the cost of providing free short-term medication supplies; surprisingly, this did not vary by hospital size or profit status, both of which may correlate with resource richness. Hospitals provide this cost assistance for many reasons. Early discontinuation of P2Y12 inhibitors is common and can be catastrophic, but also often predictable and preventable. Hospitals that improve post-discharge persistence can avoid adverse outcomes leading to costly readmissions. Assistance programs may also respond to patient need, since hospitals with assistance programs treated a higher percentage of patients with self-reported financial hardship related to medications. Finally, hospitals with pre-existing medication assistance programs were more likely to treat MI patients with higher potency P2Y12 inhibitors. This observed association may be bi-directional: higher copayment costs relative to clopidogrel may have motivated hospitals to help defray these costs, while the existence...
of assistance programs may encourage clinicians to more frequently prescribe higher-cost agents. Hospitals with pre-existing free medication programs also more frequently used other interventions to promote medication adherence, yet were not associated with higher rates of medication persistence. Potential explanations include the following: (1) These programs, while available, may have been infrequently used or suboptimally deployed and thus did not reach patients with the most potential benefit; (2) The short duration of medication support may not be sufficient to influence long-term medication persistence and outcomes; (3) ARTEMIS enrolled insured patients with prescription drug coverage, therefore the impact of pre-existing free medication programs may be underestimated. Patients without insurance may be the primary target of hospital-based free medication programs, but were not captured in our data. However, even in this insured study population, most patients in our study reported financial hardship related to medications and 17% reported recently failing to fill a medication because of cost concerns. Finally, hospitals randomized to the ARTEMIS intervention may not have used alternative free medication programs because the study intervention provided full copayment support. It is therefore important to note that pre-existing free medications programs were not associated with improved persistence even when examining only control hospitals, where patients did not receive copayment support from ARTEMIS.

We anticipated a lesser impact of the randomized copayment intervention among hospitals already providing free short-term medication assistance. However, the uptake of the randomized intervention was similar in hospitals with and without pre-existing programs, and the intervention was associated with a similar magnitude of improved persistence for patients treated in hospitals with and without pre-study free medication programs. The MI FREEE (Post-Myocardial Infarction Free RX Event and Economic Evaluation) trial randomized patients to full coverage of secondary prevention medications, resulting in 4% to 6% higher adherence rates and lower vascular event rates. Combined, these studies argue for systematic efforts to reduce long-term out-of-pocket medication costs for patients post-MI regardless of the existence of alternative hospital-based strategies. In contrast, the HeartStrong study did not improve medication adherence with a behavioral economic approach that included financial incentives for adherence. In our study, neither pre-study free medication programs nor the randomized intervention were associated with improvement in MACE rates. This is consistent with some prior randomized trials in which interventions improved adherence or persistence rates without impact on clinical outcomes. Despite this uncertain impact on clinical outcomes, a greater proportion of hospitals provided free medication programs when surveyed at the end of the study, with half of the hospitals previously without free medication programs converted to now offering free short-term medication assistance.

Medication cost remains an important consideration following MI. Patients in ARTEMIS commonly reported concerns about medication cost and financial hardship even before discharge from the MI admission. It is possible that cost-reduction programs, either through pre-existing medication assistance programs or the randomized voucher intervention, resulted in financial and quality-of-life benefits for patients that were unrelated to medication persistence or recurrent cardiovascular events. From a resource usage perspective, hospitals using these programs need to identify and target individuals at the greatest risk of cost-related non-adherence, and triage patients with non-financial adherence barriers to other supportive measures that might be more effective. Further study is needed to identify an optimal cost-reduction strategy, alone or in combination with non-financial interventions, for improving medication-taking habits and clinical outcomes.

This study has several important limitations. ARTEMIS was limited to sites in the United States and

| Outcome at 1 Y                      | Pre-Study Hospital Ability to Provide Free Medication | Intervention | Usual Care | Adjusted OR/HR (95% CI) | $P_{interaction}$ |
|------------------------------------|------------------------------------------------------|--------------|------------|------------------------|------------------|
| P2Y12 Inhibitor persistence        | Yes                                                  | 87.2%        | 83.0%      | 1.25 (0.98–1.59)       | 0.85             |
|                                   | No                                                   | 87.4%        | 84.2%      | 1.18 (0.96–1.44)       |                  |
| P2Y12 inhibitor persistence (pharmacy) | Yes                                                  | 53.6%        | 44.0%      | 1.45 (1.20–1.75)       | 0.71             |
|                                   | No                                                   | 59.0%        | 48.3%      | 1.46 (1.25–1.70)       |                  |
| MACE                               | Yes                                                  | 10.2%        | 10.3%      | 1.24 (0.98–1.57)       | 0.21             |
|                                   | No                                                   | 10.7%        | 10.8%      | 1.04 (0.86–1.27)       |                  |

HR indicates hazard ratio; MACE, major adverse cardiovascular events; and OR, odds ratio.

*Hospital reports ability to provide free P2Y12 inhibitor for a short period (30 days) to patients who cannot afford the prescribed P2Y12 inhibitor therapy, sponsored by the hospital or an external organization.
patients with US-based health insurance. The impact of cost-reduction strategies in other contexts cannot be assessed. Short-term copayment reduction could be more effective among patients without insurance coverage for prescription medication. In addition, free medication programs were identified by hospital self-report. We could not assess the quality or scope of these programs, such as patient eligibility and how drug was delivered to the patient. It is possible that these programs could be effective if delivered systematically to appropriate patients. This post hoc analysis used rigorous propensity models that encompassed a wide spectrum of patient- and hospital-level covariates, but may still be limited by unmeasured confounders. The randomized copayment voucher intervention resulted in numerically higher persistence when measured by both patient report (which was the prespecified co-primary end point of the ARTEMIS trial) and pharmacy fills, but only pharmacy fill persistence reached statistical significance after adjustment. This may be related to recall bias and overestimation of persistence by self-report. Medication persistence was measured by pharmacy fills using a linked pharmacy claims data source that encompasses the majority of US pharmacies, however, persistence may be underestimated if filled at a pharmacy that is not submitting claims data, and pharmacy fills may also misclassify persistence, though this misclassification should be non-differential and not impact the study findings.20,21

Our analysis could be biased toward the null if lower income patients who are more likely to benefit from a cost-reduction strategy are less likely to use pharmacies that participate in the Symphony Health data aggregator system. When considering both assessment methods, our results support an overall significant impact of the randomized intervention on persistence, similar to the primary ARTEMIS analysis. We were unable to specifically assess the impact of free medication programs on initiation of P2Y$_{12}$ inhibitors, since our first assessment of persistence occurred at 90 days. Finally, some sites reported changing their ability to provide free medication programs in the follow up survey at 1 year after completion of ARTEMIS enrollment. Some of these changes could have occurred during the study period, thereby biasing our analysis towards the null. For this, and the other reasons noted above, we cannot exclude the possibility that some hospital free medication programs may be effective.

CONCLUSIONS

Before participation in the ARTEMIS trial, approximately half of hospitals already offered a free short-term supply of P2Y$_{12}$ inhibitors to patients with myocardial infarction. However, patients enrolled in the ARTEMIS trial—with insurance coverage for prescription medications—at these hospitals did not have better 1-year medication persistence or MACE rates compared with patients treated at hospitals that did not offer this type of short-term medication assistance. In contrast, eliminating patient copayments for 1 year, was effective in improving persistence to P2Y$_{12}$ inhibitors in hospitals with and without pre-existing free short-term medication programs. Health systems may consider systematic and long-term strategies to reduce cost burden for their patients rather than short-term interventions.

ARTICLE INFORMATION

Received January 9, 2020; accepted March 11, 2020.

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Acknowledgments

Dr JA Doll, Ms LA Kaltenbach, and Dr TY Wang had full access to all the data in the study and take responsibility for its integrity and the data analysis. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the article, and its final contents. Author contributions: Concept and design: Drs Doll, Anstrom, Cannon, Henry, Fonarow, Choudhry, Peterson, Wang; Acquisition, analysis, or interpretation of data: Dr Doll, Ms Kaltenbach, Drs Anstrom, Cannon, Henry, Fonarow, Choudhry, Fonseca, Bhalla, Eudicone, Peterson, Wang; Drafting of the article: Doll, Wang; Statistical analysis: Kaltenbach, Anstrom; Obtained funding: Peterson, Wang.

Sources of Funding

This study was supported by a research grant from AstraZeneca to the Duke Clinical Research Institute. The trial protocol and data collection forms were designed and written by the academic investigators. Duke Clinical Research Institute, Durham, North Carolina, served as the coordinating center and was responsible for all study data collection and analyses. The sponsor reviewed this article but had no role in the data analysis.

Disclosures

Anstrom reports consulting honoraria from AstraZeneca. Cannon reports consulting honoraria from Amgen, Arisaph, Boehringer Ingehelm, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Merck, and Takeda and consulting and monitoring honoraria for Alynylam, Amarin, Amgen, Arisaph, AstraZeneca, Boehringer Ingehelm, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Janssen, Kowa, Lipmedix, Merck, Pfizer, Regeneron, Sanofi, and Takeda. Henry reported receiving a steering committee honorarium for ARTEMIS from AstraZeneca. Fonarow reports consulting honoraria from Abbott, Amgen, AstraZeneca, Bayer, Janssen, Novartis, Choudhry reported receiving research grant support to Brigham and Women’s Hospital from Merck, Sanofi, AstraZeneca, CVS Health, and Medisafe Inc. Fonseca was an employee and shareholder of AstraZeneca during the conduct of this study. Bhalla and Eudicone are employees of AstraZeneca. Peterson reported receiving grants and/or personal fees from Bayer Pharmaceuticals, Janssen Pharmaceuticals, AstraZeneca, Genentech, and the American Heart Association GWTG-Stroke Analytic and has served as a consultant/advisory board member for Janssen, Boehringer Ingehelm, Sanofi, Bayer, Merck, AstraZeneca, Signal Path, and Venable. Wang reported receiving research grant support to the Duke Clinical Research Institute.
Research Institute from AstraZeneca, Bristol-Myers Squibb, Cryolife, Pfizer, Portola, and Regeneron and receiving consulting honoraria from AstraZeneca and Sanofi. The remaining authors have no disclosures to report.

Supplementary Materials
Table S1–S3
Figure S1–S3

REFERENCES

1. Choudhry NK, Glynn RJ, Avorn J, Lee JL, Brennan TA, Reisman L, Toscano M, Levin R, Mattin GS, Antman EM, et al. Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes. Am Heart J. 2014;167:51–58.

2. Mathews R, Wang TY, Honeycutt E, Henry TD, Zettler M, Chang M, Fonarow GC, Peterson ED. Persistence with secondary prevention medications after acute myocardial infarction: insights from the TRANSLATE-ACS study. Am Heart J. 2015;170:62–69.

3. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. JAMA. 2007;297:177–186.

4. Rymer J, McCoy LA, Thomas L, Peterson ED, Wang TY. Persistence of evidence-based medication use after discharge from academic versus nonacademic hospitals among patients with non-ST-segment elevation myocardial infarction. Am J Cardiol. 2014;114:1479–1484.

5. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:e354–e426.

6. O’Gara PT, Kushner FG, Ascheim DD, Casey DE, Chandra B, Cheng MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, et al. 2013 ACCF/AHA guideline for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;127:e352–e425.

7. Amin AP, Mukhopadhyay E, Nathan S, Napan S, Kelly RF. Association of medical noncompliance and long-term adverse outcomes, after myocardial infarction in a minority and uninsured population. Circulation. 2009;115:78–89.

8. Mehran R, Barber L, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet. 2013;382:1714–1722.

9. Mathews R, Wang W, Kaltenbach LA, Thomas L, Shah RJ, Ali M, Peterson ED, Wang TY. Hospital variation in adherence rates to secondary prevention medications and the implications on quality. Circulation. 2018;137:2128–2138.

10. Ho PM, Lambert-Kerzner A, Carey EP, Fahdi IE, Bryson CL, Melenyk SD, Bosworth HB, Radcliff T, Davis R, Mun H, et al. Multifaceted intervention to improve medication adherence and secondary prevention measures after acute coronary syndrome hospital discharge: a randomized clinical trial. JAMA Intern Med. 2014;174:198–199.

11. Volpp KG, Troxel AB, Mehta SJ, Norton L, Zhu J, Lim R, Wang W, Marcus N, Terviesch C, Caldarella K, et al. Effect of electronic reminders, financial incentives, and social support on outcomes after myocardial infarction: the heartstrong randomized clinical trial. JAMA Intern Med. 2017;177:1093–1101.

12. Levy AE, Huang C, Huang A, Michal Ho P. Recent approaches to improve medication adherence in patients with coronary heart disease: progress towards a learning healthcare system. Curr Atheroscler Rep. 2016;20:5.

13. Bosworth HB, Granger BB, Mendys P, Brindis R, Burkholder R, Czajkowski SM, Daniel-JG, Ekman I, Ho M, Johnson M, et al. Medication adherence: a call for action. Am Heart J. 2011;162:412–424.

14. Doll JA, Wang TY, Choudhry NK, Cannon CP, Cohen DJ, Fonarow GC, Henry TD, Bhandary DD, Khan N, Davidson-Ray LD, et al. Rationale and design of the Affordability and Real-world Antiplalet Treatent Effectiveness after Myocardial Infarction Study (ARTEMIS): a multi-center, cluster-randomized trial of P2Y12 receptor inhibitor copayment reduction after myocardial infarction. Am Heart J. 2016;177:33–41.

15. Watson TY, Kaltenbach LA, Cannon CP, Fonarow GC, Choudhry NK, Henry TD, Cohen DJ, Bhandary D, Khan ND, Anstrom KJ, et al. Effect of medication co-payment vouchers on P2Y12 inhibitor use and major adverse cardiovascular events among patients with myocardial infarction: the ARTEMIS Randomized clinical trial. JAMA. 2019;321:44–55.

16. Krousel-Wood M, Holt E, Joyce C, Ruiz R, Dormelles A, Webber LS, Morisky DE, Frohlich ED, Re RN, He J, et al. Differences in cardiovascular disease risk when antihypertensive medication adherence is assessed by pharmacy fill versus self-report: the Cohort Study of Medication Adherence among Older Adults (CoSMO). J Hypertens. 2015;33:412–420.

17. Navar AM, Taylor B, Mulder H, Fleivitz E, Monda KL, Fleivitz A, Maya JF, Lopez JA, Peterson ED. Association of prior authorization and out-of-pocket costs with patient access to PCSK9 inhibitor therapy. JAMA Cardiol. 2017;2:1217–1225.

18. Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, Messenger JC, Khanal S, Peterson ED, Bach RJ, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMiER registry. Circulation. 2006;113:2803–2809.

19. Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeeweiss S, Toscano M, Reisman L, Fernandes J, Spettell C, Lee JL, et al. Full coverage to improve medication adherence and secondary prevention measures after myocardial infarction. N Engl J Med. 2011;365:2088–2097.

20. Choo PW, Rand CS, Inui TS, Lee ML, Cain E, Cordeiro-Breault M, Canning C, Platt R. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to anti-hypertension therapy. Med Care. 1999;37:846–857.

21. Grymonpre R, Cheang M, Fraser M, Metge C, Sitar DS. Validity of a prescription claims database to estimate medication adherence in older persons. Med Care. 2006;44:471–477.
Supplemental Material
Table S1. Variables for Propensity Score Models.

| Variable                                                                 | Variable Type                                         |
|--------------------------------------------------------------------------|-------------------------------------------------------|
| Hospital provides pre-study free medication program or randomized to intervention* | Yes/no                                                |
| Randomization scheme                                                     | Categorical (2:1 vs. 1:1 scheme)                      |
| Age                                                                      | Continuous                                            |
| Age >=65 vs. <65                                                         | Yes/no                                                |
| Male sex                                                                 | 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<sub>12</sub> inhibitor use                                      | Yes/no                                                |
| Home aspirin use                                                         | Yes/no                                                |
| Creatinine Clearance                                                     | Continuous                                            |
| Nadir hemoglobin                                                         | Yes/no                                                |
| 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 recurrent 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)            |
| Cardiac arrest                                                           | Yes/no                                                |
| 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                                                |
A separate propensity score model was developed for the “hospital provides pre-study free medication program” and the “randomized intervention” analyses. Candidate variables were identical in the two models, except that the “hospital provides pre-study medication assistance” model adjusts for randomized intervention group, while the “randomized intervention” analysis adjusts for whether hospitals provide pre-study free medication programs.
Table S2. The association of hospital use of pre-study free medication programs (vs. no free medication programs) with P2Y\textsubscript{12} inhibitor persistence and MACE among hospital randomized to the copayment intervention.

| Outcome                  | Unadjusted OR (95% C.I.) | Adjusted OR (95% C.I.) |
|--------------------------|--------------------------|------------------------|
| 90-day Persistence       |                          |                        |
| Patient report           | 1.13 (0.77-1.65)         | 1.13 (0.83-1.54)       |
| Pharmacy fill            | 0.87 (0.68-1.12)         | 0.98 (0.72-1.34)       |
| 1-year Persistence       |                          |                        |
| Patient report           | 1.04 (0.82-1.31)         | 1.11 (0.89-1.40)       |
| Pharmacy fill            | 0.89 (0.74-1.07)         | 0.97 (0.79-1.19)       |
| 1-year MACE              | 0.95 (0.72-1.26)         | 0.94 (0.74-1.18)       |
Table S3. The association of hospital use of pre-study free medication programs (vs. no free medication programs) with P2Y$_{12}$ inhibitor persistence and MACE among hospital randomized to usual care.

| Outcome                  | Unadjusted OR (95% C.I.) | Adjusted OR (95% C.I.) |
|--------------------------|--------------------------|------------------------|
| 90-day Persistence       |                          |                        |
| Patient report           | 1.08 (0.78-1.48)         | 0.99 (0.74-1.34)       |
| Pharmacy fill            | 1.04 (0.85-1.28)         | 1.00 (0.82-1.22)       |
| 1-year Persistence       |                          |                        |
| Patient report           | 0.95 (0.76-1.19)         | 0.92 (0.74-1.14)       |
| Pharmacy fill            | 0.94 (0.79-1.12)         | 0.92 (0.77-1.09)       |
| 1-year MACE              | 0.95 (0.74-1.20)         | 0.94 (0.75-1.17)       |
Figure S1. Distribution of the predicted probability of being treated at a hospital with a free medication program.
Figure S2. Distribution of the predicted probability of being treated at a hospital randomized to intervention.

- Propensity score among patients treated at hospitals randomized to intervention
- Propensity score among patients treated at hospitals randomized to control
Figure S3. MACE cumulative incidence among ARTEMIS hospitals.