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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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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.

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Key Words: medication adherence ■ myocardial infarction ■ quality improvement

Medication non-adherence after myocardial infarction (MI) is common and is associated with adverse cardiovascular outcomes.[1–4] Guidelines recommend $P2Y_{12}$ inhibitors for at least 1 year after an MI,[5,6] but premature discontinuation of $P2Y_{12}$ inhibitors can lead to stent thrombosis and

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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 payors 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

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 mediation 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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,"

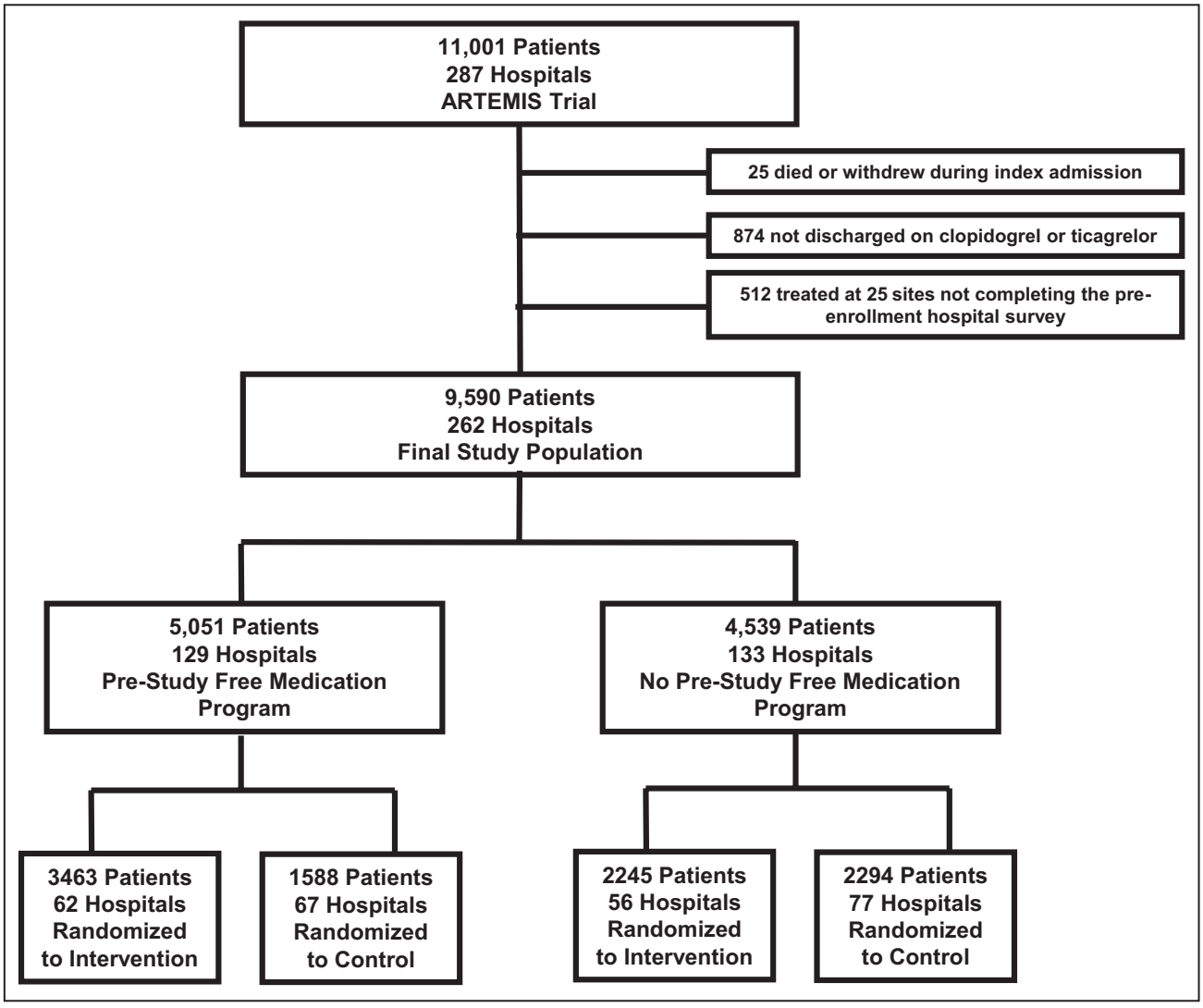

Figure 1. Study population.
ARTEMIS indicates Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study trial.

"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.

$P2Y_{12}$ inhibitor persistence, measured by patient report, and MACE were co-primary end points of the ARTEMIS study. As patient report overestimates medication persistence,[16] persistence was also defined as no gap in $P2Y_{12}$ 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. $P2Y_{12}$ 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 $P2Y_{12}$ 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.

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 payor			0.29
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
$P2Y_{12}$ inhibitor use*			
Home $P2Y_{12}$ 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
Financial hardship related to medications	51%	49%	0.05
Not filled prescription because of cost in past 90 d	17%	17%	0.49

CABG indicates coronary artery bypass graft; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segement–elevation myocardial infarction; and TIA, transient ischemic attack.

*All patients were treated during hospitalization with clopidogrel and/or ticagrelor (switching during the hospitalization was permitted), and clopidogrel or ticagrelor at time of discharge.

persistence (Table 4). 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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 $P2Y_{12}$ inhibitors copayments for the guideline-recommeneded 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

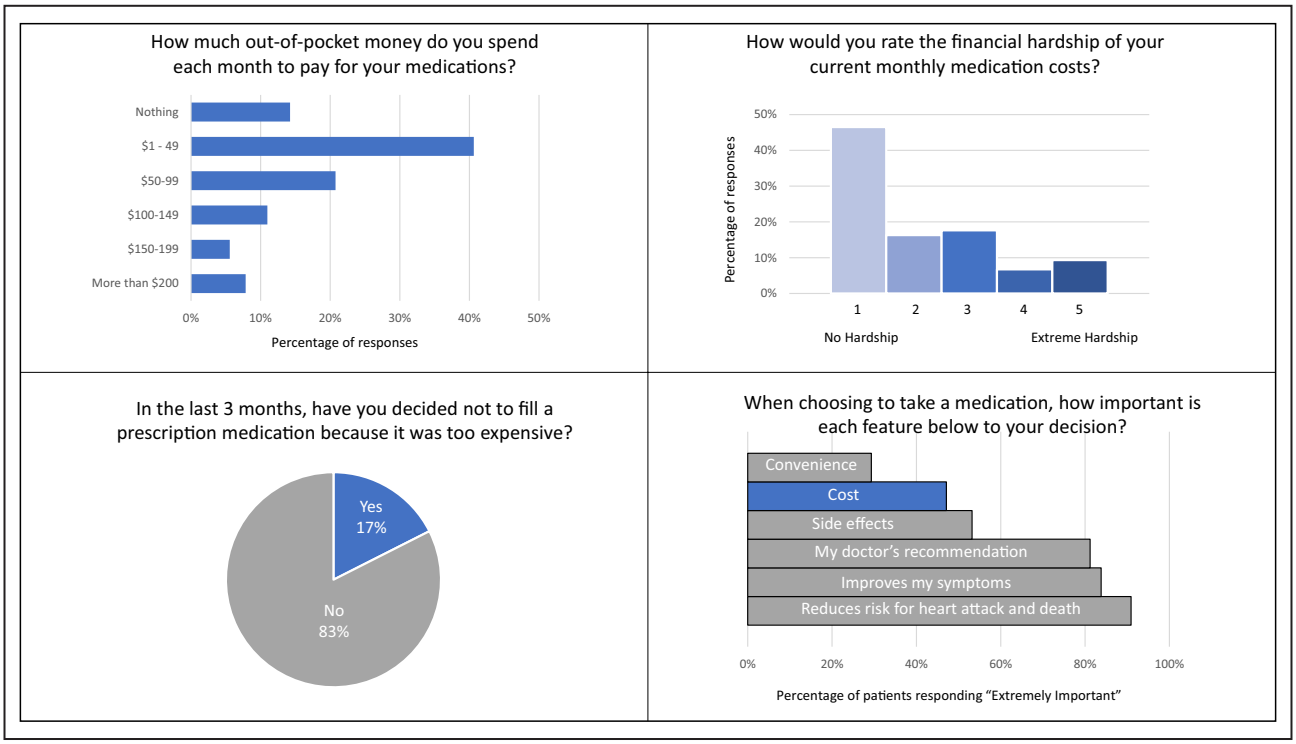

Figure 2. Responses to the baseline patient survey on medication cost and cost-related non-adherence, administered to all subjects at time of enrollment in ARTEMIS (The Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) (n=9590).

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 $P2Y_{12}$ inhibitors is common and can be catastrophic,[8,18] 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 $P2Y_{12}$ 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

Table 3. The Association of Hospital Use of Pre-Study Free Medication Programs (Vs No Free Medication Programs) With $P2Y_{12}$ 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 (0.85–1.19)	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)
Outcome	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**
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.

Table 4. The Association of the Randomized Copayment Reduction Intervention With Outcomes Among Patients Treated at Hospitals With and Without Pre-Existing Free Medication Programs

Outcome at 1 Y	Pre-Study Hospital Ability to Provide Free Medication*	Intervention	Usual Care	Adjusted OR/HR (95% CI)	$P_{interaction}$
$P2Y_{12}$ Inhibitor persistence (patient-report)	Yes	87.2%	83.0%	1.25 (0.98–1.59)	0.85
	No	87.4%	84.2%	1.18 (0.96–1.44)	
$P2Y_{12}$ 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 $P2Y_{12}$ inhibitor for a short period (30 days) to patients who cannot afford the prescribed $P2Y_{12}$ inhibitor therapy, sponsored by the hospital or an external organization.

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 inteventions 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.[19] 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.[11] 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.[10,15] 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

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

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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.

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Supplementary Materials

Table S1–S3
Figure S1–S3

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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 $P2Y_{12}$ inhibitor use	Yes/no
Home aspirin use	Yes/no
Creatinine Clearance	Continuous
Nadir hemoglobin	Continuous
Multivessel disease	Yes/no
Access Site	Categorical (Femoral vs. other)
PCI performed	Categorical (multivessel vs. culprit vs. none)
CABG performed	Yes/no
Drug-eluting stent implanted	Yes/no
In-hospital or prior bleeding	Yes/no
In-hospital 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

Site: Total bed size	Continuous
Site: Teaching Status	Yes/no
Site: Government hospital	Yes/no
Site: Member of a Healthcare Network	Yes/no
Site: Surgery Capabilities	Yes/no

*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 $P2Y_{12}$ 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)
	Unadjusted HR (95% C.I.)	**Adjusted HR (95% C.I.)**
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)
	Unadjusted HR (95% C.I.)	**Adjusted HR (95% C.I.)**
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.

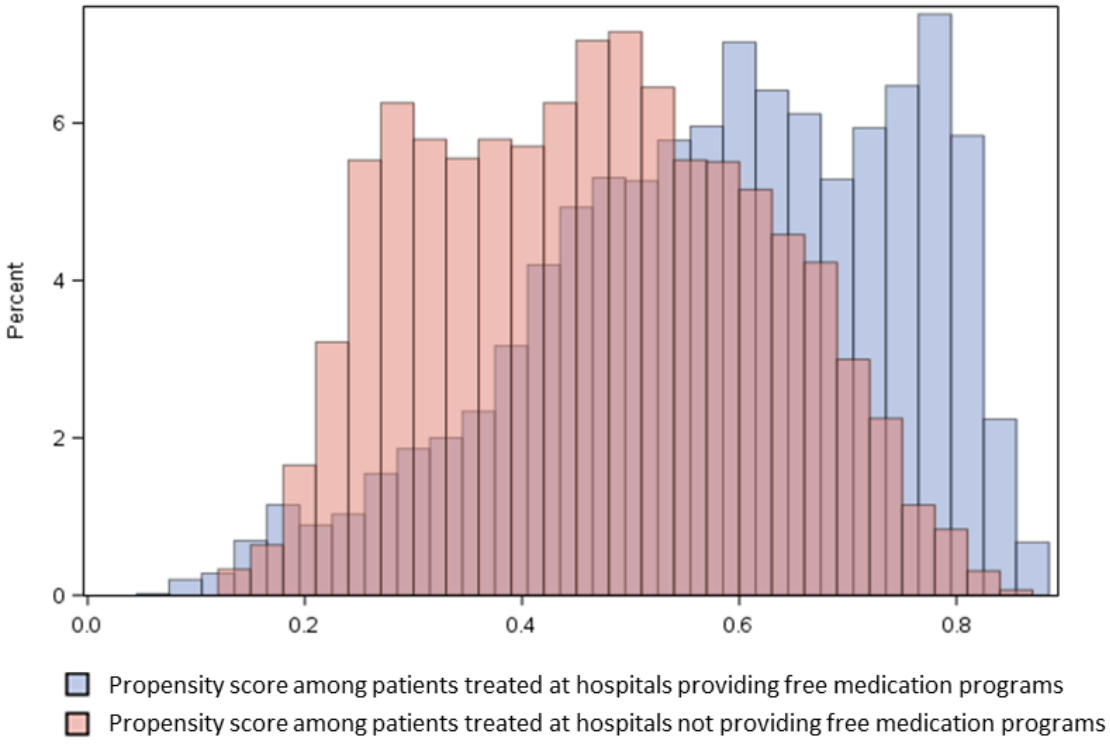

Figure S2. Distribution of the predicted probability of being treated at a hospital randomized to intervention.

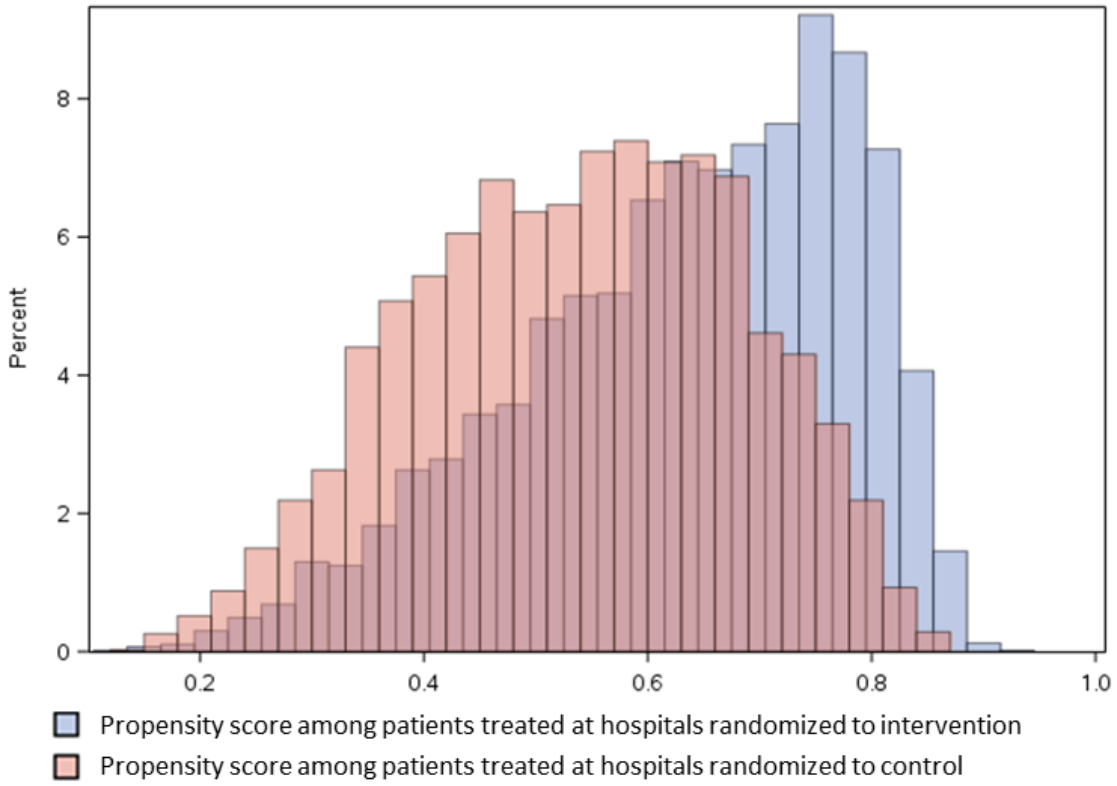

Figure S3. MACE cumulative incidence among ARTEMIS hospitals.