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ORIGINAL ARTICLE

Copayment Reduction Voucher Utilization and Associations With Medication Persistence and Clinical Outcomes

Findings From the ARTEMIS Trial

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BACKGROUND: Cost is frequently cited as a barrier to optimal medication use, but the extent to which copayment assistance interventions are used when available, and their impact on evidence-based medication persistence and major adverse cardiovascular events is unknown.

METHODS AND RESULTS: The ARTEMIS trial (Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) randomized 301 hospitals to usual care versus the ability to provide patients with vouchers that offset copayment costs when filling $P2Y_{12}$ inhibitors in the 1 year post-myocardial infarction. In the intervention group, we used multivariable logistic regression to identify patient and medication cost characteristics associated with voucher use. We then used this model to stratify both intervention and usual care patients by likelihood of voucher use, and examined the impact of the voucher intervention on 1-year $P2Y_{12}$ inhibitor persistence (no gap in pharmacy supply >30 days) and major adverse cardiovascular events (all-cause death, myocardial infarction, or stroke). Among 10 102 enrolled patients, 6135 patients were treated at hospitals randomized to the copayment intervention. Of these, 1742 (28.4%) never used the voucher, although 1729 (99.2%) voucher never-users filled at least one $P2Y_{12}$ inhibitor prescription in the 1 year post-myocardial infarction. Characteristics most associated with voucher use included: discharge on ticagrelor, planned 1-year course of $P2Y_{12}$ inhibitor treatment, white race, commercial insurance, and higher out-of-pocket medication costs (c-statistic 0.74). Applying this propensity model to stratify all enrolled patients by likelihood of voucher use, the intervention improved medication persistence the most in patients with high likelihood of voucher use (adjusted interaction P=0.03, odds ratio, 1.86 [95% CI, 1.48–2.33]). The intervention did not significantly reduce major adverse cardiovascular events in any voucher use likelihood group, although the odds ratio was lowest (0.86 [95% CI, 0.56–1.16]) among patients with high likelihood of voucher use (adjusted interaction P=0.04).

CONCLUSIONS: Among patients discharged after myocardial infarction, those with higher copayments and greater out-of-pocket medication costs were more likely to use a copayment assistance voucher, but some classes of patients were less likely to use a copayment assistance voucher. Patients at low likelihood of voucher use benefitted least from copayment assistance, and other interventions may be needed to improve medication-taking behaviors and clinical outcomes in these patients.

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

Key Words: hospitals ■ medication adherence ■ myocardial infarction ■ stroke ■ ticagrelor

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WHAT IS KNOWN

- Copayment assistance programs via vouchers that reduce or eliminate copayments at the time of pharmacy fill reduce the likelihood of prescription abandonment and nonpersistence.
- $P2Y_{12}$ inhibitor copayment vouchers, compared with usual care, improved persistence with $P2Y_{12}$ inhibitors in the ARTEMIS (Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) randomized controlled trial, but 28% of patients in the intervention arm did not use the provided copayment assistance voucher.

WHAT THE STUDY ADDS

- Prescription of ticagrelor, as compared with clopidogrel, on hospital discharge was the patient characteristic most strongly associated with study voucher use; planned 1-year course of $P2Y_{12}$ inhibitor treatment, white race, commercial insurance, and higher out-of-pocket medication costs were also associated with voucher use.
- The copayment assistance voucher intervention improved medication persistence and reduced major adverse cardiovascular events most in patients at highest likelihood of voucher use.

In the United States, patients with healthcare insurance are paying an increasingly larger share of the costs of their care through high deductible healthcare plans or rising copayments for office visits or medications.[1,2] Although a number of new agents have been shown to reduce cardiovascular events in patients with atherosclerotic disease, increased cost sharing has become a barrier to the initiation of and persistence with these evidence-based medications.[3–8] For patients with financial barriers to treatment, copayment assistance programs via vouchers that reduce or eliminate copayments at the time of pharmacy fill have been used to reduce the likelihood of prescription abandonment and nonpersistence.[9]

Recently, the ARTEMIS (Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) trial randomized hospitals to usual care versus the ability to eliminate patients' $P2Y_{12}$ inhibitor copayments after acute myocardial infarction (MI). In intention-to-treat analyses, the intervention improved guideline-adherent treatment selection and longitudinal medication persistence but did not reduce cardiovascular events.[10] However, 28% of patients in the intervention arm chose not to use the copayment vouchers provided. Understanding patient factors associated with voucher use could enable organizations operating under a value-based payment structure to identify patients at low likelihood of voucher use for whom alternate interventions are needed to improve medication persistence and outcomes. We, therefore, performed a post hoc, secondary analysis of the ARTEMIS trial to identify patient and hospital factors associated with likelihood of copayment voucher use. We then evaluated the effect of the copayment assistance intervention (versus usual care) on medication persistence and major adverse cardiovascular events (MACE) in patients stratified by likelihood of voucher use.

METHODS

The data, analytic methods, and study materials used in this article will not be made available to other researchers.

Data Source and Patient Population

The design and primary results of the ARTEMIS trial have been previously published.[10,11] Briefly, ARTEMIS was a multi-center, cluster-randomized clinical trial that randomized 301 hospitals to usual care or to the copayment assistance intervention—the ability to provide patients with vouchers that offset copayment costs when patients filled ticagrelor or clopidogrel prescriptions in the year post-MI. The coprimary end points of the trial were 1-year $P2Y_{12}$ inhibitor persistence and MACE (composite of death, recurrent MI, or stroke).

Patients were enrolled from June 2015 to September 2016. Eligible patients were ≥18 years old, diagnosed with ST-segment elevation MI or non–ST-segment elevation MI, discharged on a $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor), had United States-based health insurance coverage with a prescription drug benefit, and were able to provide written informed consent for longitudinal follow-up. Patients with prior intracranial hemorrhage, contraindications to $P2Y_{12}$ inhibitor therapy at discharge, enrollment in another research study that specified the type and duration of $P2Y_{12}$ inhibitor in the 1 year post-MI, life expectancy <1 year, or plans to move outside of the United States in the next year were excluded from enrollment in the trial. ARTEMIS enrolled 11 001 patients. Since this analysis was focused on identifying patient and hospital factors associated with voucher use and the effect of voucher use on postdischarge medication adherence and outcomes, we excluded patients who died or withdrew from the study before index discharge (n = 28) and those who were not discharged on clopidogrel or ticagrelor (n = 961).

All patients enrolled in ARTEMIS provided written informed consent, and the study protocol was approved by the institutional review board of each participating site. The Duke University Medical Center Institutional Review Board approved use of ARTEMIS data for this analysis.

Data Collection and Definitions

Patient-reported $P2Y_{12}$ inhibitor persistence and MACE were coprimary end points of the ARTEMIS study. Patient-reported persistence was validated 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.[12] For this analysis, persistence was defined as no gap in $P2Y_{12}$ inhibitor supply

>30 days by pharmacy fill data. MACE was defined as the composite of all-cause death, recurrent MI, or stroke, which were centrally adjudicated by independent medical record review according to standard definitions.[11]

Statistical Analysis

In the intervention arm, patients were identified as voucher users or nonusers. To identify hospital characteristics associated with voucher use, we determined the proportion of patients at each site that ever used the copayment assistance voucher and divided hospitals into those with high voucher use (≥70% of patients used the voucher) and low voucher use (<70%). We describe characteristics of each group of hospitals, using proportions for categorical variables and medians with 25th and 75th quartiles for continuous variables. Differences between voucher use groups were tested using χ^2 tests for categorical variables and Kruskal-Wallis tests for continuous variables.

Among patients in the intervention arm, we reported the overall proportion of patients that never used a copayment assistance voucher and, among these patients, the reasons they provided for not using the voucher. Among voucher nonusers, we reported the proportion that reported stopping $P2Y_{12}$ inhibitor within 30 days after discharge as they had fewer opportunities to use a voucher than patients who continued >30 days. We describe baseline characteristics of voucher users and nonusers, using proportions for categorical variables and medians with 25th and 75th quartiles for continuous variables. Differences between groups were tested using χ^2 tests for categorical variables and Kruskal-Wallis tests for continuous variables.

Among intervention arm patients, we then estimated the probability of voucher use conditional on observed covariates using multivariable logistic regression with voucher use as the dependent variable and the baseline covariates as independent variables. Baseline covariates included in the model were selected by expert opinion and review of the peer-reviewed literature for factors associated with nonadherence, based on a possible association with voucher use, and included demographic and socioeconomic variables, self-reported past prescription-taking behavior, medical history, and details of the index MI (Methods I in the Data Supplement). We tested the discrimination of the model using the c-statistic, validated it by bootstrapping with n=1000 bootstrap samples, and report a 95% CI. Intervention arm patients were divided into tertiles by likelihood of voucher use. We then applied the estimated coefficients from the logistic regression model to patients in the usual care arm to obtain the probability of voucher use among these patients, then applied the tertile cutoffs from the intervention arm patients to the entire population to obtain populations at high, intermediate, and low likelihood of voucher use, for which we described baseline characteristics. The distribution of propensity scores for the intervention and usual care arms are shown in Figure I in the Data Supplement.

To determine the effect of the $P2Y_{12}$ inhibitor copayment assistance intervention on 90-day and 1-year persistence with $P2Y_{12}$ inhibitor therapy by tertile of likelihood for voucher use, we used logistic regression with generalized estimating equations to account for within hospital clustering, including terms for likelihood of voucher use (high, intermediate, or low) and the interaction between likelihood of voucher use and treatment assignment (intervention or usual care). As in the primary ARTEMIS analysis, to account for differences between patients enrolled at intervention and usual care hospitals, we adjusted for selected patient characteristics (Methods II in the Data Supplement) as well as a propensity score for being in the intervention arm. We report the interaction between treatment assignment and voucher use on 90-day and 1-year $P2Y_{12}$ inhibitor persistence, as well as the unadjusted and adjusted effect of the intervention on patients at high, intermediate, or low likelihood of voucher use. We repeated this analysis for time to first MACE event, using a Cox proportional hazards model instead of logistic regression.

We imputed missing socioeconomic variables, lab values, and weight- to age-, gender-, and race-specific modes for categorical variables and medians for continuous variables. Missing data related to medical history, home medications, admission features, and in-hospital events were imputed to the mode. For each variable included in models, <5% of patients had missing data for all variables except for intended duration of $P2Y_{12}$ inhibitor (missing in 27% of patients) and Symphony copayment amount (missing in 16%). Symphony copayment amount was imputed using discharge $P2Y_{12}$ inhibitor, age ≥65, and insurance specific medians. All analyses were performed by statisticians at the Duke Clinical Research Institute using SAS version 9.4.

RESULTS

In the ARTEMIS trial, 10 102 patients were discharged alive on either clopidogrel or ticagrelor. Of the 6135 patients discharged from intervention arm hospitals, 1742 (28.4%) never used the provided copayment assistance voucher in the 1 year after discharge. Intervention arm hospitals had a median voucher use rate of 71.4% (25th, 75th percentiles: 59.7%, 78.6%) among enrolled patients (Figure 1). Annual MI volume, ticagrelor use before study start, total hospital beds, teaching hospital status, and region were similar

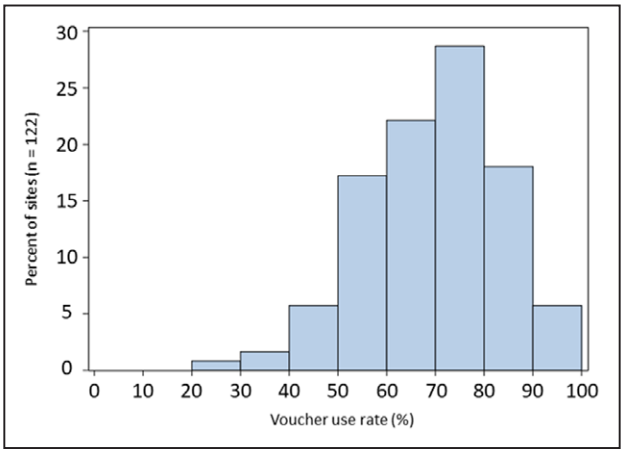

Figure 1. Distribution of site-specific rates of voucher use.
Intervention arm hospitals had a median voucher use rate of 71.4% (25th, 75th percentiles: 59.7%, 78.6%) among enrolled patients.

between low and high voucher use hospitals (Table I in the Data Supplement).

Nearly all intervention arm patients filled a $P2Y_{12}$ inhibitor prescription after discharge and thus had an opportunity to use the voucher; 6092 (99.3%) patients filled a prescription within 30 days after receiving the voucher. Among the 1742 patients who never used the voucher, 134 (7.7%) died, 159 (9.1%) withdrew from the study, and 96 (5.5%) had stopped taking their $P2Y_{12}$ inhibitor within 30 days of discharge. An additional 398 patients (22.8%) had technical barriers to voucher use, including rejection of the voucher by the pharmacy, losing the voucher, forgetting to use the voucher, or not knowing how to use the voucher. Despite study voucher support, such as replacing lost or nonfunctioning cards and contacting pharmacies if a patient complained that the voucher was not honored, these patients remained nonusers through 1 year post-MI. The remaining patients either said they had no need for the voucher (n=372, 21.4%) or gave no reason for voucher nonuse (n=568, 32.6%). Almost all of these voucher nonusers (n=1729, 99.2%) filled at least 1 prescription for a $P2Y_{12}$ inhibitor in the 1 year post-MI.

Baseline characteristics of intervention arm patients who used and did not use the voucher are presented in Table II in the Data Supplement. On multivariable analysis, the variable most strongly associated with voucher use was the type of $P2Y_{12}$ inhibitor prescribed at hospital discharge; prescription of ticagrelor was associated with significantly higher likelihood of study voucher use (82.2% versus 54.1% for generic clopidogrel) (Table 1). Additionally, higher overall out-of-pocket medication expense, higher $P2Y_{12}$ inhibitor copayment, new prescription of $P2Y_{12}$ inhibitor (ie, not taking before MI hospitalization), and patient awareness of a 1-year planned course of $P2Y_{12}$ inhibitor therapy at discharge were also associated with higher likelihood of voucher use. Patients who self-reported pre-MI medication nonadherence were less likely to use the voucher, whereas patients who rated cost as an important factor for medication decision-making were more likely to use the voucher. Although the voucher could be used regardless of insurance type, patients with Medicare or Medicaid insurance were less likely to use the voucher, as well as patients who were of nonwhite race, unemployed, or unmarried. The c-statistic for the model was 0.74 (95% CI, 0.73–0.76).

Table 1. Variables Significantly Associated With Voucher Use Among Intervention Arm Patients

	Wald χ^2	OR (95% CI)
Generic $P2Y_{12}$ inhibitor prescribed	339.9	0.30 (0.26–0.34)
Medicaid insurance (vs commercial)	49.2	0.46 (0.37–0.57)
Length of hospitalization for index MI (per 1 day increase)	32.9	0.93 (0.91–0.95)
Nonwhite race	30.0	0.59 (0.48–0.71)
New prescription for $P2Y_{12}$ inhibitor	27.5	1.64 (1.35–1.96)
Unemployed (vs full or part-time employed)	16.0	0.73 (0.63–0.85)
Self-reported overall out-of-pocket medication expenses	14.4	
$0		0.69 (0.57–0.84)
$1–$49		1.00 (reference)
$50–$99		1.05 (0.89–1.25)
$100–$149		1.23 (0.98–1.53)
$150–$199		1.45 (1.06–1.99)
≥$200		1.13 (0.89–1.45)
Self-reported medication nonadherence*	13.0	0.79 (0.69–0.89)
Medicare insurance (vs commercial)	9.9	0.78 (0.67–0.91)
Consented into study on day of discharge	8.7	1.21 (1.06–1.38)
$P2Y_{12}$ inhibitor copayment amount (per $50 increase)	8.2	1.13 (1.04–1.23)
Planned ≥1 y course of $P2Y_{12}$ inhibitor at discharge	7.9	1.79 (1.19–2.68)
Unmarried	6.9	0.83 (0.73–0.95)
Self-reported importance of cost in medication decision-making†	4.5	1.16 (1.01–1.32)

Other variables in the model that were not significant included age, sex, health literacy, depression, education level, mail order pharmacy use, previously not filled a medication due to cost, difficulty accessing pharmacy previously to fill medication, previous receipt of free medication/samples, PCI (multivessel, single vessel, no PCI), prior MI, tobacco use, in-hospital heart failure, cardiogenic shock, or cardiac arrest, total number of medications prescribed at discharge, discontinued $P2Y_{12}$ medication within 30 days. Model C index =0.74. MI indicates myocardial infarction; and OR, odds ratio.

*Patient-reported ever missed taking a dose of any prescribed medication in the 4 wk before MI.

†Patient rated medication cost as extremely important in medication decision-making using a 5-point scale.

Baseline Characteristics and Outcomes by Likelihood of Voucher Use

Using the coefficients from the multivariable model, patients were then divided into 3 groups by likelihood of voucher use: 4163 patients (41.2%) were at low likelihood of voucher use (≤67% predicted likelihood of voucher use), 3091 (30.6%) at intermediate likelihood (67%–85% predicted likelihood of voucher use), and 2848 (28.2%) at high likelihood (≥85% likelihood of voucher use). Compared with patients at high likelihood of voucher use, patients at low likelihood of voucher use were older, and more often female, nonwhite, unmarried, unemployed, and nonprivately insured. Patients at low likelihood of voucher use had a greater burden of comorbidities, including prior MI, prior stroke, prior heart failure, peripheral arterial disease, and diabetes mellitus, and were more often taking a $P2Y_{12}$ inhibitor before admission. They less often presented with ST-segment elevation MI and less frequently had percutaneous coronary intervention performed during the index hospitalization (Table 2).

Table 2. Baseline Characteristics Among Patients at High, Intermediate, and Low Likelihood of Voucher Use

Patient Characteristics	Low Likelihood (n=4163)	Intermediate Likelihood (n=3091)	High Likelihood (n=2848)	*P* Value
Age	64 (55–72)	62 (54–70)	60 (53–67)	<0.001
Male gender	2469 (59.3)	2143 (69.3)	2263 (79.5)	<0.001
White race	3352 (80.5)	2774 (89.7)	2785 (97.8)	<0.001
Hispanic ethnicity	187 (4.5)	137 (4.4)	86 (3.0)	0.004
Married	2159 (51.9)	1999 (64.7)	2254 (79.1)	<0.001
Employed	1195 (28.7)	1460 (47.2)	1974 (69.3)	<0.001
College graduate	1920 (46.1)	1531 (49.5)	1479 (51.9)	<0.001
Commercial health insurance	1939 (46.6)	2005 (64.9)	2460 (86.4)	<0.001
Prior MI	1160 (27.9)	590 (19.1)	310 (10.9)	<0.001
Prior PCI	1427 (34.3)	737 (23.8)	398 (14.0)	<0.001
Prior CABG	670 (16.1)	298 (9.6)	160 (5.6)	<0.001
Prior stroke/TIA	443 (10.6)	165 (5.3)	72 (2.5)	<0.001
Prior heart failure	541 (13.0)	176 (5.7)	67 (2.4)	<0.001
End-stage renal disease on dialysis	146 (3.5)	34 (1.1)	14 (0.5)	<0.001
Peripheral artery disease	404 (9.7)	153 (4.9)	77 (2.7)	<0.001
Hypertension	3182 (76.4)	2114 (68.4)	1682 (59.1)	<0.001
Diabetes mellitus	1642 (39.4)	940 (30.4)	703 (24.7)	<0.001
Current/recent smoker	1476 (35.5)	1021 (33.0)	876 (30.8)	<0.001
Weight, kg	87 (74–102)	88 (76–103)	91 (80–105)	<0.001
Transfer in to ARTEMIS hospital during index MI admission	1365 (32.8)	966 (31.3)	863 (30.3)	0.08
STEMI	1634 (39.3)	1502 (49.6)	1502 (52.7)	<0.001
New prescription for $P2Y_{12}$ inhibitor	3098 (74.4)	2767 (89.5)	2787 (97.9)	<0.001
Aspirin before index MI	2131 (51.2)	1259 (40.7)	982 (34.5)	<0.001
Creatinine clearance on admission, mL/min	63 (45–83)	71 (54–89)	77 (62–93)	<0.001
Nadir hemoglobin during index admission, mg/dL	12.5 (11.8–14.3)	13.2 (11.8–14.3)	13.7 (12.6–14.7)	<0.001
Multivessel disease	2037 (48.9)	1392 (45.0)	1258 (44.2)	<0.001
PCI type				<0.001
Multivessel	919 (22.1)	783 (25.3)	656 (25.0)	
Single vessel	2402 (57.7)	2111 (68.3)	2132 (74.9)	
None	842 (20.2)	197 (6.4)	60 (2.1)	
Drug-eluting stent implanted (among PCI patients)	2823 (85.0)	2657 (91.8)	2645 (94.9)	<0.001
CABG performed for index MI	143 (3.4)	10 (0.3)	1 (0.0)	<0.001
In-hospital or prior bleeding	178 (4.3)	77 (2.5)	35 (1.2)	<0.001
In-hospital recurrent MI	22 (0.5)	19 (0.6)	17 (0.)	0.88
In-hospital stroke	23 (0.6)	3 (0.1)	2 (0.1)	<0.001
Cardiogenic shock during index admission	143 (3.4)	94 (3.0)	76 (2.7)	0.19
Heart failure during index admission	563 (13.5)	261 (8.4)	130 (4.6)	<0.001
Cardiac arrest during index admission	109 (2.6)	92 (3.0)	67 (2.4)	0.32
Cardiac rehab referral	2301 (55.3)	1912 (61.9)	2002 (70.3)	<0.001
Low health literacy (score <10)	738 (17.7)	413 (13.4)	290 (10.2)	<0.001
Baseline angina frequency				<0.001
No angina (SAQ AF 100)	1427 (34.3)	1183 (38.3)	1156 (40.6)	
Monthly angina (SAQ AF 70–90)	1775 (42.6)	1360 (44.0)	1240 (43.5)	
Daily weekly angina (SAQ AF 0–60)	945 (22.7)	544 (17.6)	446 (15.7)	

(*Continued*)

Table 2. Continued

Patient Characteristics	Low Likelihood (n=4163)	Intermediate Likelihood (n=3091)	High Likelihood (n=2848)	*P* Value
Depression (PHQ-2 >3)	627 (15.1)	341 (11.0)	198 (7.0)	<0.001
EuroQOL VAS	70 (50–80)	70 (50–80)	75 (60–85)	<0.001
Self-reported financial hardship				<0.001
No hardship	1806 (43.4)	1283 (41.5)	1113 (39.1)	
Low/some hardship	1176 (28.2)	961 (31.1)	926 (32.5)	
Moderate/extreme hardship	849 (20.4)	512 (16.6)	417 (14.6)	
Self-reported medication nonadherence*	1327 (31.9)	771 (24.9)	508 (17.8)	<0.001

ARTEMIS indicates Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study; CABG, coronary artery bypass grafting surgery; MI, myocardial infarction; PCI, percutaneous coronary intervention; PHQ-2, Patient Health Questionnaire-2; SAQ AF, Seattle Angina Questionnaire Angina Frequency score; STEMI, ST-segment elevation MI; TIA, transient ischemic attack; and VAS, visual analogue scale.

*Patient-reported ever missed taking a dose of any prescribed medication in the 4 wk before MI.

On unadjusted analyses, patients at low likelihood of voucher were more often nonpersistent with $P2Y_{12}$ inhibitor therapy at 1 year following the index MI than those at intermediate and high likelihood of voucher use (53.7% versus 47.4% versus 41.6%, *P*<0.001). Patients at low likelihood of voucher use also had a higher incidence of MACE at 1 year than those at intermediate and high likelihood of voucher use (16.2% versus 8.3% versus 4.4%, *P*<0.001), as well as a higher incidence of death (6.7% versus 2.5% versus 1.3%, *P*<0.001), MI (10.7% versus 6.1% versus 3.2%, *P*<0.001), and stroke (1.5% versus 0.6% versus 0.4%, *P*<0.001; Table III in the Data Supplement). After adjustment for baseline factors, patients at low and intermediate likelihood of voucher use had a higher incidence of MACE than those at high likelihood of voucher use (hazards ratio [HR], 2.91 [95% CI, 2.37–3.57] for low versus high; HR, 1.63 [95% CI, 1.31–2.02] for intermediate versus high).

Impact of the Intervention Stratified by Likelihood of Voucher Use

Within each tertile, baseline covariates were similar between patients in the randomized intervention and usual care arms (Table IV in the Data Supplement). Unadjusted persistence at 90 days was significantly higher in intervention arm patients compared with usual care patients at high (78.9% [intervention] versus 68.9% [usual care], *P*<0.001), intermediate (74.1% [intervention] versus 70.2% [usual care], *P*=0.03), and low (70.6% [intervention] versus 65.0% [usual care], *P*<0.001) likelihood of voucher use. A similar pattern was observed at 1 year (high likelihood: 62.4% [intervention] versus 48.0% [usual care], *P*<0.001; intermediate: 54.2 [intervention] versus 49.5% [usual care], *P*=0.02; low: 48.5% [intervention] versus 44.1% [usual care], *P*=0.009; Figure 2). The unadjusted interaction between the intervention and likelihood of voucher use was significant when examining 1 year (*P*=0.02) but not 90-day medication persistence (*P*=0.15). After adjustment, 90-day and 1-year persistence were higher among intervention arm patients than among usual care patients in all 3 voucher use categories, but patients at high likelihood of voucher use had the greatest odds of persistence at 90 days and at 1 year (odds ratio for 1-year persistence, intervention versus usual care: 1.25 [95% CI, 1.05–1.47] in low likelihood, 1.31 [1.10–1.56] for intermediate likelihood, and 1.86 [1.48–2.33] for high likelihood). The interaction remained nonsignificant at 90 days (*P*=0.15) and significant at 1 year (*P*=0.03).

The unadjusted incidence of MACE was higher in the intervention arm among patients at low (17.4% versus 15.0%, *P*=0.09) and intermediate (9.4% versus 6.1%, *P*=0.003) likelihood of voucher use, but lower among patients at high (4.1% versus 5.3%, *P*=0.17) likelihood of voucher use (Figure 3); the interaction between the intervention and likelihood of voucher use was significant when examining 1-year MACE (*P*=0.02). After adjustment for baseline characteristics, the *P* for interaction remained statistically significant at 0.04 for 1-year MACE; however, the risk of MACE significantly differed between intervention and usual care only for intermediate voucher use likelihood patients (low: HR, 1.17 [95% CI, 0.98–1.39]; intermediate: HR, 1.58 [95% CI, 1.18–2.11]; and high: HR, 0.80 [95% CI, 0.56–1.16]).

DISCUSSION

In the ARTEMIS cluster-randomized trial, 28% of patients in the intervention arm never used the copayment assistance voucher even though nearly all intervention arm patients filled a prescription for a $P2Y_{12}$ inhibitor at least once. Patients prescribed a nongeneric $P2Y_{12}$ inhibitor were more likely to use the voucher, as were those with higher out-of-pocket medication costs and a 1-year planned course of $P2Y_{12}$ inhibitor therapy. Younger age, white race, private insurance, and employment were associated with higher voucher use. When we examined the trial population as a whole, the intervention (randomization to copay reduction) had the

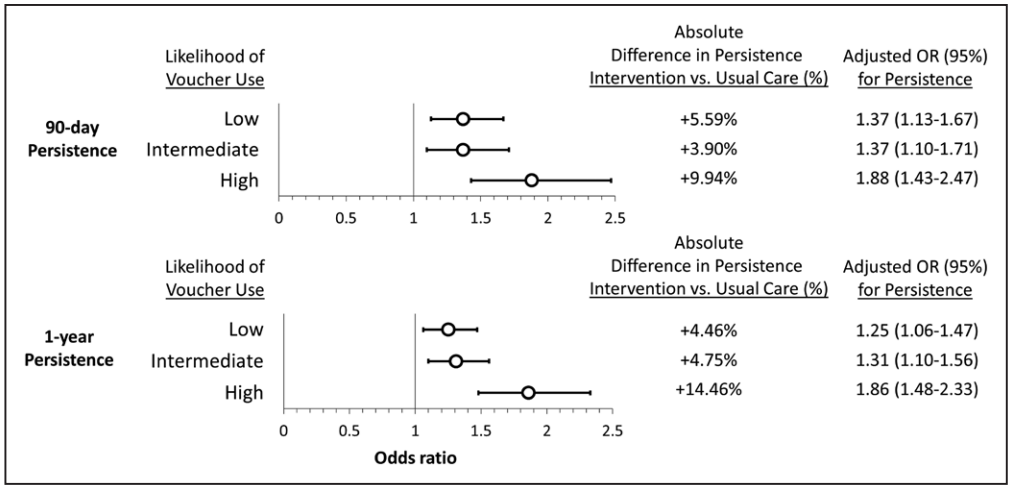

Figure 2. Effect of copayment intervention on $P2Y_{12}$ inhibitor persistence by likelihood of voucher use.
Compared with usual care, the copayment intervention increased 90-day and 1-year persistence in patients at high, intermediate, and low likelihood of voucher use, but the effect was greatest among patients at high likelihood of voucher use (adjusted *P* interaction =0.15 at 90 days, 0.03 at 1 y). Among low likelihood patients, 2024 were discharged from intervention and 2123 from usual care hospitals; among intermediate and high likelihood hospitals, 2024 and 2071 were discharged from intervention hospitals, and 1067 and 777 from usual care hospitals, respectively. OR indicates odds ratio.

largest effect on patients at high likelihood of voucher use; among these patients, the intervention improved 1-year persistence by 86% (compared with 25% for low likelihood patients) and reduced 1-year MACE by 20% (compared with a 17% increase in low likelihood patients). This analysis identifies a population of patients for whom interventions beyond copayment assistance vouchers are needed to improve medication persistence and clinical outcomes. Although the discrimination of the multivariable model for identifying likelihood of voucher use was only moderate, to our knowledge, this article is the first to model likelihood of copayment assistance voucher use. The discrimination of the model is in line with models used to identify likelihood of other important patient behaviors, such as medication adherence and missed clinic appointments.[13–17]

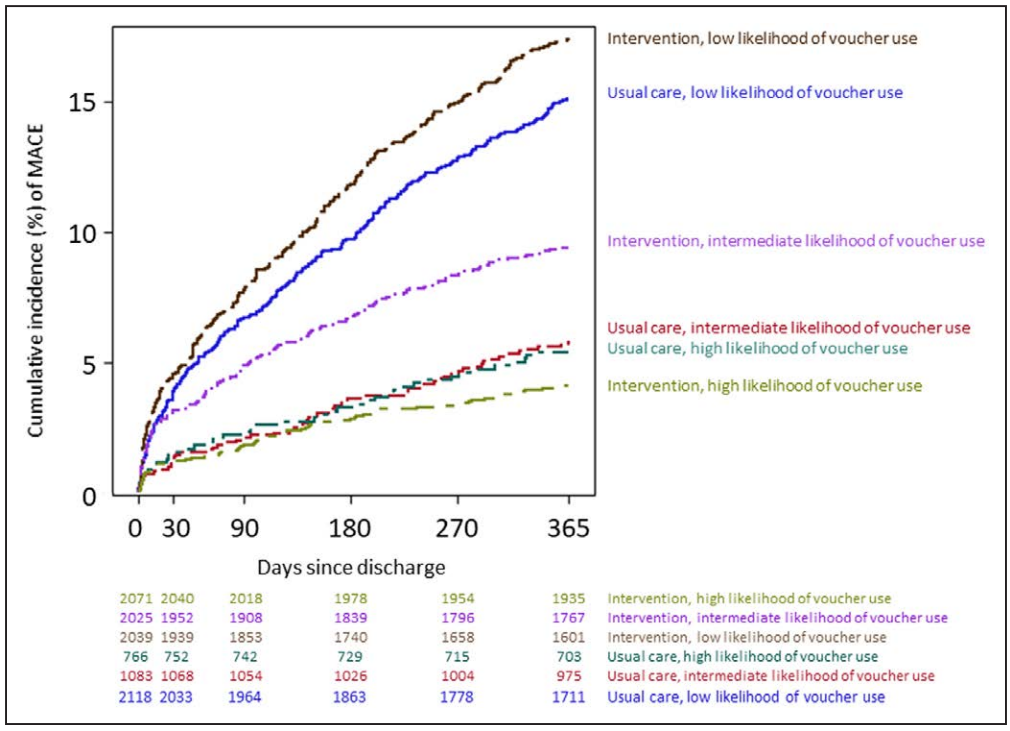

Figure 3. Effect of copayment intervention on major adverse cardiovascular events by likelihood of voucher use.
Compared with those discharged from usual care hospitals, patients at low and intermediate likelihood of voucher use discharged from copayment intervention hospitals had a higher cumulative incidence of major adverse cardiovascular events (MACE); patients at high likelihood of voucher use discharged from copayment intervention hospitals had a lower cumulative incidence of MACE.

Vouchers are commonly used to subsidize specific healthcare services, especially in developing countries.[18] They are particularly useful as a tool to target subsidies to particular populations, such as those that are most in need of the service or those that stand to derive the most benefit, with high sensitivity and specificity.[19] As opposed to some other mechanisms of subsidizing healthcare services, vouchers enable patients a greater degree of choice with regard to when and where they receive the healthcare service, but they are vulnerable to the possibility that some patients will not redeem the voucher at all. In a survey conducted in Kenya, vouchers that significantly defray the cost of family planning and childcare delivery were used by <25% of eligible women, with nonusers citing multiple obstacles to voucher use.[20] Despite suboptimal utilization, financial assistance vouchers have increased access to critical healthcare services and improved outcomes.[21] Experience with voucher programs in high-income countries is limited, with most research focusing on food or housing assistance for low-income families or individuals.[22,23] In a United States-based program providing smokers with vouchers for nicotine replacement therapy, 70% of those provided with vouchers redeemed them.[24]

By contrast, ARTEMIS evaluated a medication copayment voucher program in a relatively resource-rich environment, although there was substantial heterogeneity among voucher recipients with regard to the nonsubsidized cost of the prescribed $P2Y_{12}$ inhibitor and their ability to pay. Higher voucher use in patients discharged on ticagrelor (compared with clopidogrel) and those with higher $P2Y_{12}$ inhibitor copayments and overall out-of-pocket medication costs reflects the sensitivity of voucher use to perceived or actual benefits of using the voucher; for patients with low $P2Y_{12}$ inhibitor copayments, any inconvenience associated with voucher use may have overwhelmed the small financial benefit. The strong association between prescription of ticagrelor at discharge and voucher use also explains why fewer patients at usual care hospitals (to whom ticagrelor was only prescribed 36% of the time, compared with 55% at intervention hospitals)[10] were at high likelihood of voucher use.

However, some categories of patients that might be expected to have limited financial resources, including nonwhite patients, unemployed patients, and those with government insurance, were also less likely to use vouchers, even after adjusting for $P2Y_{12}$ inhibitor copayment. These groups of patients are less likely to be adherent to post-MI medications[25,26] and have substantial room to benefit from an intervention that improves persistence, such as copayment assistance vouchers.[10] Using a copayment assistance voucher adds another layer of complexity to a healthcare system difficult for many patients to navigate. To use a copayment assistance voucher, patients have to understand and recall the purpose of the voucher (along with other post hospital discharge instructions) and remember to bring it to the pharmacy each time they fill a $P2Y_{12}$ inhibitor prescription. Lower voucher use in patients with longer index hospital stays (a marker of greater severity of illness, comorbidity, and frailty) may also reflect these patients' difficulty with more complex health care transactions. A simpler mechanism of reducing copayments, such as one applied automatically without need for patients to present a voucher, may have been easier for these patients to use. However, this type of mechanism cannot readily be deployed in the multipayer, multipharmacy, multihealth record structure that exists in the United States today.

Developing easy-to-use copayment assistance mechanisms may be particularly important in light of this study's findings with respect to the effect of the copayment assistance program stratified by likelihood of voucher use. Compared with usual care, the intervention had the greatest effect on medication persistence in the subgroup of patients at high likelihood of voucher use. With a more universally used copayment assistance program, the benefits seen in patients at high likelihood of voucher use might have translated to a broader population.

Even within a value-based system devoting resources to encouraging medication persistence, lower medication costs remain associated with medication-taking behavior.[27] Voucher-based copayment assistance programs may be one way to lower medication costs and improve persistence to expensive medications; however, from the perspective of an organization implementing such program, patients at low and intermediate likelihood of voucher use are unlikely to be receptive to or derive substantial benefit, wasting resources expended and necessitating other measures to improve their medication persistence and outcomes. From the standpoint of an organization operating under a value-based payment framework, these patients might derive greater benefit from more intensive services to help them navigate the healthcare system and understand the importance of medication adherence, such as structured educational interventions and frequent points of contact with members of the healthcare team.[28–30] Such services could include structured education about how to use copayment assistance vouchers, when available, for patients who may be otherwise unlikely to use them.

Limitations

There are several limitations to this study. ARTEMIS was a cluster-randomized clinical trial, and there were baseline differences in the characteristics of patients enrolled at copayment assistance intervention and usual care hospitals. It is uncertain how well the propensity model for voucher use, developed in the intervention arm, performs in the distinct usual care population. The fact that

more intervention arm patients were at high likelihood of voucher use than usual care arm patients, although a greater proportion of usual care arm patients had baseline characteristics associated with medication persistence, suggests unadjusted analyses grouping patients by likelihood of voucher use may be biased toward finding no difference between the intervention and control arms. Analyses were adjusted for measured differences in a wide spectrum of patient and hospital characteristics; however, unmeasured confounders likely still exist. Measured baseline characteristics are unlikely to capture all patient characteristics associated with the decision to use a medication copayment voucher, and there may be a healthy user bias associated with voucher use. The difference in distribution of propensity scores between the intervention and usual care arm also reduces the effective sample size when stratifying by propensity score, biasing results toward the null. In addition, we did not capture whether patients in the usual care group used nonstudy copayment assistance vouchers. The present analysis reports a subgroup analysis of a clinical trial with a neutral effect on one of its coprimary end points, raising concerns about the interpretation of any single *P* value. Nevertheless, the analysis was hypothesis-driven, and the effects of the copayment intervention on $P2Y_{12}$ inhibitor persistence and MACE by likelihood of voucher use are directionally consistent. Last, it is uncertain whether an approach using baseline characteristics to identify patients at low likelihood of voucher use and target adjunctive therapies for medication persistence to those patients would be successful if implemented prospectively; however, our results could inform such a design.

Conclusions

Among patients discharged after MI, those patients with higher copayments and greater out-of-pocket medication costs were more likely to use a copayment assistance voucher, but some classes of patients—including older patients, nonwhite patients, unemployed patients, and those with government insurance—were less likely to use a copayment assistance voucher. Patients at high likelihood of voucher use benefitted the most from copayment assistance; for these patients, assignment to the intervention arm was associated with a greater increase in medication persistence. For patients at lower likelihood of copayment voucher use, other interventions are needed to improve medication persistence and clinical outcomes.

ARTICLE INFORMATION

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