Title

Does the Effectiveness of a Medicine Copay Voucher Vary by Baseline Medication Out-Of-Pocket Expenses? Insights From ARTEMIS

Journal

Journal of the American Heart Association, 11(20)

ISSN

2047-9980

Authors

Rymer, Jennifer A
Kaltenbach, Lisa A
Peterson, Eric D
et al.

Publication Date

2022-10-18

DOI

10.1161/jaha.122.026421

Peer reviewed

Journal of the American Heart Association

ORIGINAL RESEARCH

Does the Effectiveness of a Medicine Copay Voucher Vary by Baseline Medication Out-Of-Pocket Expenses? Insights From ARTEMIS

Jennifer A. Rymer, MD, MBA, MHS; Lisa A. Kaltenbach, MS; Eric D. Peterson, MD, MPH; David J. Cohen, MD, MSc; Gregg C. Fonarow, MD; Niteesh K. Choudhry, MD, PhD; Timothy D. Henry, MD; Christopher P. Cannon, MD; Tracy Y. Wang, MD, MHS, MSc

BACKGROUND: Persistence to P2Y12 inhibitors after myocardial infarction (MI) remains low. Out-of-pocket cost is cited as a factor affecting medication compliance. We examined whether a copayment intervention affected 1-year persistence to P2Y12 inhibitors and clinical outcomes.

METHODS AND RESULTS: In an analysis of ARTEMIS (Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study), patients with MI discharged on a P2Y12 inhibitor were stratified by baseline out-of-pocket medication burden: low ($0–$49 per month), intermediate ($50–$149 per month), and high (≥$150 per month). The impact of the voucher intervention on 1-year P2Y12 inhibitor persistence was examined using a logistic regression model with generalized estimating equations. We assessed the rates of major adverse cardiovascular events among the groups using a Kaplan–Meier estimator. Among 7351 MI-treated patients at 282 hospitals, 54.2% patients were in the low copay group, 32.0% in the middle copay group, and 13.8% in the high copay group. Patients in higher copay groups were more likely to have a history of prior MI, heart failure, and diabetes compared with the low copay group (all $P<0.0001$). Voucher use was associated with a significantly higher likelihood of 1-year P2Y12 inhibitor persistence regardless of copayment tier (low copay with versus without voucher: adjusted odds ratio [OR], 1.44 [95% CI, 1.25–1.66]; middle copay: adjusted OR, 1.63 [95% CI, 1.37–1.95]; high copay group: adjusted OR, 1.41 [95% CI, 1.05–1.87]; P interaction=0.42). Patients in the high copay group without a voucher had similar risk of 1-year major adverse cardiovascular events compared with patients in the high copay group with a voucher (adjusted hazard ratio, 0.89 [95% CI, 0.66–1.21]).

CONCLUSIONS: Medication copayment vouchers were associated with higher medication persistence at 1 year following an MI, regardless of out-of-pocket medication burden.

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

Key Words: copay ■ myocardial infarction ■ persistence ■ voucher

The American College of Cardiology/American Heart Association guidelines recommend at least 1 year of dual antiplatelet therapy after an acute myocardial infarction (MI).[1] Despite these recommendations, adherence and persistence to oral P2Y12 inhibitors after MI remains low.[2–4] Indeed, nearly one third of patients are no longer persistent with at least 1 of their post-MI medications by 6 months after discharge, and nearly 50% are no longer taking these medications 1 year after discharge.[2–4] Premature discontinuation of oral P2Y12 inhibitors is

Correspondence to: Jennifer A. Rymer, MD, MBA, Duke University Medical Center, 2301 Erwin Road, Durham, NC 27705. Email: jennifer.rymer@duke.edu

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026421

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The use of medication copayment vouchers is associated with improved medication persistence after myocardial infarction.
- Copayment assistance alone does not appear to improve postmyocardial infarction clinical outcomes, even in patients with high copayment burden.

What Are the Clinical Implications?

- As use of a copayment voucher is not associated with a larger impact in terms of postmyocardial infarction medication persistence in patients with a higher copayment burden compared with those with a lower copayment burden, copayments should not be reserved for patients with high copayment burden.

Nonstandard Abbreviations and Acronyms

ARTEMIS	Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study
BARC	Bleeding Academic Research Consortium
MACE	major adverse cardiovascular events
MI FREEE	Post-Myocardial Infarction Free Rx Event and Economic Evaluation

associated with an increased risk of cardiovascular morbidity and mortality.[5,6] Some commonly cited reasons for poor medication persistence are out-of-pocket costs and the inability to afford the often numerous medications added after an MI.[7,8] Increased out-of-pocket costs and cost sharing with the patient have been shown to be barriers to medication persistence across a variety of disease states and patient populations, in addition to cardiovascular diseases.[9–11]

ARTEMIS (Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) was a cluster-randomized trial that showed improved 1-year P2Y12 inhibitor persistence when patients who had an MI were given a copayment voucher that offset medication copayment costs.[12] In the current post hoc analysis, we examined whether the impact of copayment intervention on 1-year persistence to P2Y12 inhibitors and outcomes varied as a function of baseline medication out-of-pocket expense burden. We hypothesized that the copay intervention would have a larger impact in patients with a higher copayment burden compared with those with a lower copayment burden. Our analysis will further assess whether there is a particular patient population based on copayment burden that may benefit most from a copay intervention or voucher.

METHODS

The current study was supported by a research grant from AstraZeneca to the Duke Clinical Research Institute, Durham, North Carolina. The authors are solely responsible for the design and conduct of the study, all study analyses, drafting and editing of the article, and its final contents. The authors declare that all supporting data are available within the article and its online supplementary files. The Duke University Medical Center institutional review board approved the use of ARTEMIS data for this analysis.

Data Source and Patient Population

The design and results of ARTEMIS (NCT02406677) have been previously published.[12] ARTEMIS was a multicenter, cluster-randomized controlled trial, conducted from June 2015 to September 2016, in which 301 hospitals were randomized to a P2Y12 inhibitor copayment reduction program versus usual care. The P2Y12 inhibitor copayment reduction intervention involved vouchers to offset the copayment costs of ticagrelor and clopidogrel (treatment selection was at the discretion of the physician) in the year after MI. ARTEMIS examined the effect of this intervention on 1-year medication persistence and clinical outcomes.

Eligible patients included those aged ≥18 years who presented with a non–ST-segment–elevation MI (NSTEMI) or ST-segment–elevation MI (STEMI), were discharged on an oral P2Y12 inhibitor, had US-based healthcare coverage with prescription drug coverage, and could provide informed consent. Patients with prior intracranial hemorrhage, contraindications to P2Y12 inhibitor therapy at discharge, enrollment in another research study that specified the type and duration of P2Y12 inhibitor in the 1 year following MI, life expectancy <1 year, or plans to move outside of the United States in the next year were excluded. For the current analysis, there were 8329 patients discharged alive on clopidogrel or ticagrelor with a postdischarge prescription fill in the Symphony Health Solutions database within 1 year of discharge. Symphony Health Solutions captures pharmacy fill data from ≈90% of retail, 60% of mail-order, and 70% of specialty pharmacies in the United States.[11] We excluded 978 patients with missing or "do not know" responses to the baseline question asked of trial participants regarding out-of-pocket costs for medications. Table S1 describes the baseline characteristics of the excluded patients compared with

the final study population. The final study population included 7351 patients at 282 sites.

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 the current analysis.

Study End Points and Definitions

The primary study end points included 1-year oral P2Y12 inhibitor persistence, which was defined as continued oral P2Y12 inhibitor use without a gap in prescription fills ≥30 days, and 1-year major adverse cardiovascular events (MACE), defined as a composite of death, recurrent MI, or stroke. Persistence was examined using prescription fill data from the Symphony Health Solutions database. In this analysis, we also examined the individual components of MACE, as well as Bleeding Academic Research Consortium (BARC) 3+ bleeding, which includes overt bleeding with a hemoglobin drop of <5 g/dL, transfusion with overt bleeding, cardiac tamponade, bleeding requiring surgical intervention, bleeding requiring intravenous vasoactive agents, or intracranial hemorrhage.

We stratified patients by copayment tiers according to their responses to a question on the baseline questionnaire that asked, "How much out-of-pocket money do you spend approximately each month to pay for your medications?" The low copay tier was prospectively classified for these analyses as those patients who responded that they paid $0 to $49 per month; the middle copay tier included those who paid $50 to $149 per month, and the high copay tier included those who paid ≥$150 per month. The copay tiers were created based on thresholds as listed above, which we found allowed for balanced groups of patients. The study groups included the following: low copay group without the voucher (reference group), middle copay group without the voucher, high copay without the voucher, low copay with the voucher, middle copay with the voucher, and high copay with the voucher.

Statistical Analysis

We compared the baseline patient and hospital characteristics among the following groups: low, middle, and high self-reported copay groups. Categorical variables are presented as frequencies with percentages, and the differences between the groups were assessed using chi-square or Fisher exact tests. Continuous variables are presented as medians with interquartile ranges with comparisons between the study groups performed using Wilcoxon rank sum test.

We also examined rates of oral P2Y12 inhibitor persistence among the study groups. Rates are presented as frequencies (percentages) and the differences in persistence among the study groups was assessed using a logistic regression model with generalized estimating equations to account for within-hospital clustering. We adjusted for age, non-White race versus white race, male sex, private versus nonprivate insurance, employment, education (college graduate or higher versus less than college), baseline financial hardship, history of prior MI, coronary artery bypass grafting, stroke/transient ischemic attack, peripheral artery disease, diabetes, hypertension, current/recent smoking, presentation with STEMI versus NSTEMI, home P2Y12 inhibitor use, creatinine clearance, femoral artery access versus other access, performance of percutaneous coronary intervention (multivessel percutaneous coronary intervention versus culprit only versus none), coronary artery bypass grafting performed, and drug-eluting stent used.

We also assessed rates of clinical events among the study groups using a Kaplan–Meier estimator. Differences in rates of clinical events among the study groups were assessed using a Cox proportional hazards model with robust standard errors to account for within-hospital clustering and to adjust for covariates selected a priori. We adjusted for the same covariates as were used to adjust for differences in P2Y12 inhibitor persistence. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc).

RESULTS

Among 7351 patients presenting with MI at 282 sites, there were 3983 (54.2%) patients in the low copay group, 2350 (32.0%) in the middle copay group, and 1018 (13.8%) in the high copay group. Table 1 describes the differences in baseline clinical and hospital characteristics among the low, middle, and high copay groups. Patients who had a high copay were older compared with patients in the lower copay groups (65 versus 64 versus 61 years, respectively; $P<0.0001$). Patients with a high copay were less likely to have Medicaid compared with the lower copay groups (3.0% versus 4.0% versus 13.5%, respectively; $P<0.0001$). Additionally, patients in the high copay group were significantly more likely to have various clinical comorbidities, such as history of prior MI, prior percutaneous coronary intervention, prior coronary artery bypass grafting, heart failure, diabetes, hypertension, and hyperlipidemia compared with the lower copay groups (all $P<0.0001$). Before admission, patients in the high copay group were significantly more likely to be taking a P2Y12 inhibitor compared with those in the lower copay groups.

Table 1. Baseline Patient Characteristics Stratified by Copayment Group

Variable	Overall (N=7351)	Low Copay (n=3983)	Middle Copay (n=2350)	High Copay (n=1018)	*P* value
Demographics					
Age, median (25th–75th), y	62 (54–70)	61 (53–69)	64 (55–71)	65 (57–72)	<0.0001
Women	2433 (33.1)	1311 (32.9)	800 (34.0)	322 (31.6)	0.37
Hispanic	262 (3.6)	161 (4.0)	75 (3.2)	26 (2.6)	0.04
Black	748 (10.2)	446 (11.2)	204 (8.7)	98 (9.6)	0.005
Insurance payor					
Private	4667 (63.5)	2435 (61.1)	1582 (67.3)	650 (63.9)	<0.0001
Medicare	3223 (43.8)	1583 (39.7)	1085 (46.2)	555 (54.5)	<0.0001
Medicaid	660 (9.0)	537 (13.5)	93 (4.0)	30 (3.0)	<0.0001
Financial hardship					<0.0001
None	3275 (44.6)	2513 (63.1)	645 (27.4)	117 (11.5)	
Extreme	638 (8.7)	155 (3.9)	236 (10.0)	247 (24.3)	
Employed full-time	2773 (37.7)	1575 (39.5)	884 (37.6)	314 (30.8)	<0.0001
Education					0.008
Graduated high school	2644 (36.0)	1410 (35.4)	865 (36.8)	369 (36.3)	
College	2792 (38.0)	1520 (38.2)	875 (37.2)	397 (39.0)	
Income, $					<0.0001
≤10000	490 (6.7)	368 (9.2)	93 (4.0)	29 (2.9)	
10001–20000	708 (9.6)	407 (10.2)	197 (8.4)	104 (10.2)	
20001–30000	785 (10.7)	361 (9.1)	283 (12.0)	141 (13.9)	
30001–50000	1078 (14.7)	534 (13.4)	374 (15.9)	170 (16.7)	
50001–70000	815 (11.1)	417 (10.5)	277 (11.8)	121 (11.9)	
70001–100000	709 (9.6)	367 (9.2)	253 (10.8)	89 (8.7)	
1000001–150000	511 (7.0)	295 (7.4)	163 (6.9)	53 (5.2)	
≥150001	317 (4.3)	164 (4.1)	104 (4.4)	49 (4.8)	
Prefer not to answer income questions	1937 (26.4)	1069 (26.8)	606 (25.8)	262 (25.7)	
Medical history					
Prior MI	1581 (21.5)	674 (16.9)	578 (24.6)	329 (32.3)	<0.0001
Prior PCI	1968 (26.8)	817 (20.5)	734 (31.2)	417 (41.0)	<0.0001
Prior CABG	862 (11.7)	348 (8.7)	318 (13.5)	196 (19.3)	<0.0001
Prior stroke/TIA	510 (6.9)	225 (5.7)	179 (7.6)	106 (10.4)	<0.0001
PAD	477 (6.5)	201 (5.1)	168 (7.2)	108 (10.6)	<0.0001
Heart failure	592 (8.1)	223 (5.6)	223 (9.5)	146 (14.3)	<0.0001
Diabetes	2528 (34.4)	1003 (25.2)	931 (39.6)	594 (58.4)	<0.0001
Hypertension	5296 (72.0)	2588 (65.0)	1848 (78.6)	860 (84.5)	<0.0001
Hyperlipidemia	4497 (61.2)	2150 (54.0)	1608 (68.4)	739 (72.6)	<0.0001
ESRD on dialysis	145 (2.0)	64 (1.6)	50 (2.1)	31 (3.1)	0.01
P2Y12 inhibitor use before admission	1128 (15.3)	452 (11.4)	389 (16.6)	297 (28.2)	<0.0001
In-hospital characteristics					
STEMI	3323 (45.2)	1961 (49.2)	966 (41.1)	396 (38.9)	<0.0001
Killip class III/IV	237 (3.2)	108 (2.7)	88 (3.8)	41 (4.0)	<0.0001
Catherization performed	7217 (98.2)	3918 (98.4)	2305 (98.1)	994 (97.6)	0.28
PCI performed	6538 (88.9)	3587 (90.1)	2070 (88.1)	881 (86.5)	0.002
In-hospital events					
MACE	56 (0.76)	29 (0.73)	17 (0.72)	10 (0.98)	0.68

(*Continued*)

Table 1. Continued

Variable	Overall (N=7351)	Low Copay (n=3983)	Middle Copay (n=2350)	High Copay (n=1018)	*P* value
Bleeding event	136 (1.9)	75 (1.9)	43 (1.8)	18 (1.8)	0.97
Recurrent MI	36 (0.5)	19 (0.5)	13 (0.6)	4 (0.4)	0.82
Heart failure	398 (5.4)	193 (4.9)	142 (6.0)	63 (6.2)	0.06
Cardiac arrest	185 (2.5)	112 (2.8)	57 (2.4)	16 (1.6)	0.07
Stroke	20 (0.3)	10 (0.3)	4 (0.2)	6 (0.6)	0.09
Discharge P2Y12 inhibitor prescribed					0.15
Clopidogrel	3455 (47.0)	1831 (46.0)	1138 (48.4)	486 (47.7)	
Ticagrelor	3896 (53.0)	2152 (54.0)	1212 (51.6)	532 (52.3)	
Discharge location					
Home	7153 (97.3)	3877 (97.3)	2289 (97.4)	987 (97.0)	0.65
Other acute care hospital	33 (0.4)	14 (0.3)	14 (0.6)	5 (0.5)	
Skilled nursing facility	29 (0.4)	17 (0.4)	10 (0.4)	2 (0.2)	
Extended care/rehabilitation	112 (1.5)	61 (1.5)	30 (1.3)	21 (2.1)	
Against medical advice	3 (0.04)	3 (0.08)	0	0	
Hospice	1 (0.01)	1 (0.03)	0	0	

Data are presented as number (percentage) unless otherwise indicated. CABG indicates coronary artery bypass grafting; ESRD, end-stage renal disease; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and TIA, transient ischemic attack.

Differences in Rates of Oral P2Y12 Inhibitor Persistence Between Copay Groups

Observed 1-year P2Y12 inhibitor persistence rates were 54.1%, 51.5%, and 47.8% in the low, middle, and high copay groups, respectively (*P*<0.01). Table 2 compares the rates of persistence across study groups referenced to the low copay group treated at hospitals not randomized to provide a voucher, as well as within strata (ie, high copay with voucher versus high copay without voucher). All copay groups with a voucher had a significantly higher rate of P2Y12 inhibitor persistence compared with the same-level copay group without a voucher (reference) or when compared with the low copay group without a voucher (Table 2). There was no difference in rates of P2Y12 inhibitor persistence for the high copay group without a voucher (43.0% versus 49.5%; adjusted odds ratio [OR], 0.98 [95% CI, 0.76–1.26]) and the middle copay group without a voucher (44.6% versus 49.5%; adjusted OR, 0.89 [95% CI, 0.75–1.05]), compared with the low copay group without a voucher. There was no evidence of effect modification based on the level of copay burden (*P* for interaction=0.42).

Differences in Clinical Event Rates Between Copay Groups

Observed rates of MACE within 1 year were 17.1%, 11.3%, and 8.5% for patients with high, middle, and low copayments, respectively (*P*<0.0001). Rates of BARC 3+ bleeding were 1.8%, 1.9%, and 1.3% for patients with high, middle, and low copayments, respectively (*P*<0.0001). The Figure illustrates the cumulative incidence of MACE and BARC 3+ bleeding events (95% CI) in the first year after MI for both the intervention (voucher) arm and the usual care (without a voucher)

Table 2. Association Between Copayment and Voucher Status and 1-Year Persistence to an Oral P2Y12 Inhibitor

Study group (vs within-strata copay group without a voucher or low copay group without a voucher)	Persistence, no./No. (%)	Adjusted OR (95% CI)	Adjusted *P* value
Low copay group with a voucher vs low copay group without a voucher	1387/2428 (57.1) vs 769/1555 (49.5)	1.44 (1.25–1.66)	<0.0001
Middle copay group with a voucher vs middle copay group without a voucher	799/1428 (56.0) vs 411/922 (44.6)	1.63 (1.37–1.95)	<0.0001
High copay group with a voucher vs high copay without a voucher	315/618 (51.0) vs 172/400 (43.0)	1.41 (1.05–1.87)	0.02
High copay group with a voucher vs low copay group without a voucher	315/618 (51.0) vs 769/1555 (49.5)	1.38 (1.10–1.71)	0.005
Middle copay group with a voucher vs low copay group without a voucher	799/1428 (56.0) vs 769/1555 (49.5)	1.45 (1.22–1.73)	<0.0001
Middle copay group without a voucher vs low copay group without a voucher	411/922 (44.6) vs 769/1555 (49.5)	0.89 (0.75–1.05)	0.17
High copay group without a voucher vs low copay without a voucher	172/400 (43.0) vs 769/1555 (49.5)	0.98 (0.76–1.26)	0.86

OR indicates odds ratio.

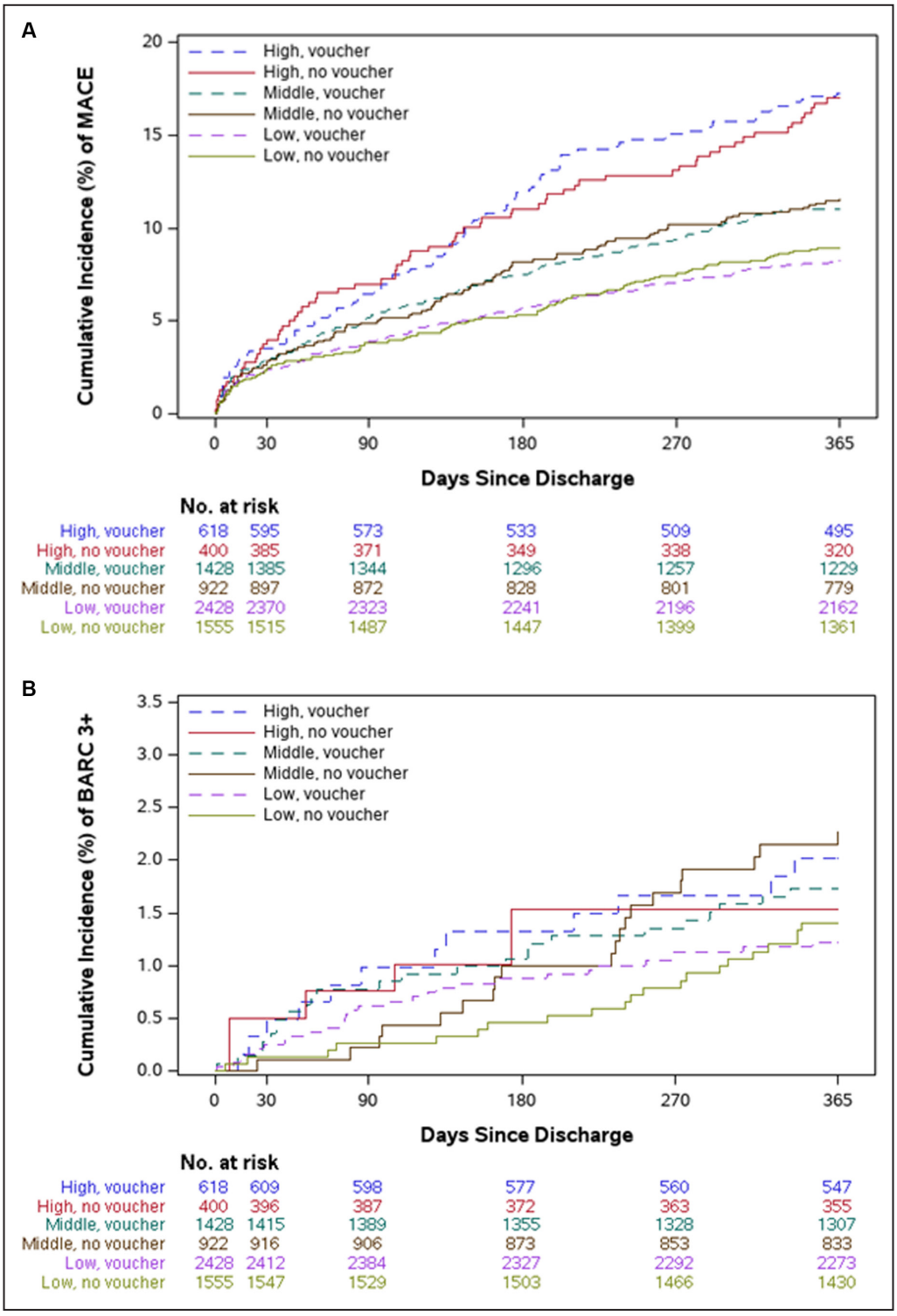

Figure 1. Cumulative incidence of clinical outcomes by study groups (copay status and intervention vs usual care).
(**A**) Cumulative incidence of major adverse cardiovascular events (MACE) after discharge for myocardial infarction (MI) by study groups (copay status and intervention vs usual care). (**B**) Cumulative incidence of Bleeding Academic Research Consortium (BARC) 3+ bleeding after discharge for MI by study groups (copay status and intervention vs usual care).

Table 3. Association Between Copayment and Voucher Status and Risk of Clinical Events

Outcome	Study group	Observed rates, %	Adjusted HR (95% CI)	Adjusted *P* value
MACE	Low copay group with a voucher vs low copay group without a voucher	8.2 vs 8.9	1.01 (0.80–1.27)	0.93
	Middle copay group with a voucher vs middle copay group without a voucher	11.1 vs 11.6	1.08 (0.85–1.37)	0.52
	High copay group with a voucher vs high copay group without a voucher	17.3 vs 17.0	1.12 (0.82–1.52)	0.46
BARC 3+ bleeding	Low copay group with a voucher vs low copay group without a voucher	1.2 vs 1.4	0.95 (0.57–1.61)	0.86
	Middle copay group with a voucher vs middle copay group without a voucher	1.7 vs 2.3	0.82 (0.45–1.50)	0.53
	High copay group with a voucher vs high copay group without a voucher	2.0 vs 1.5	1.40 (0.55–3.55)	0.47

BARC indicates Bleeding Academic Research Consortium; HR, hazard ratio; and MACE, major adverse cardiovascular events.

arm, stratified by copay status (low, middle, high). Table 3 compares the rates of various clinical events between various study subgroups (low copay group with a voucher, middle copay group with a voucher, and high copay group with a voucher) and the reference group (same-level copay group without a voucher). Patients in the high copay group without a voucher had similar risk of MACE within 1 year of discharge compared with patients in the high copay group with a voucher (17.0% versus 17.3%; adjusted hazard ratio [HR], 0.89 [95% CI, 0.66–1.21]). However, patients in the high copay group with a voucher were significantly more likely to have a MACE within 1 year of discharge compared with the reference group (low copay group without a voucher) (17.3% versus 8.9%; adjusted HR, 1.37 [95% CI, 1.02–1.83]). There were no other significant differences in the rates of any of the clinical end points (MACE or BARC 3+) when comparing the other study groups with the low copay group with no voucher. Despite greater 1-year persistence of P2Y12 inhibitor in all of the copayment groups, bleeding risks were not significantly different within copay strata.

DISCUSSION

Using data from ARTEMIS, we examined the association between copayment assistance on 1-year persistence to oral P2Y12 inhibitors as well as outcomes, including MACE and bleeding events. Patients who reported having high out-of-pocket costs were older and significantly more likely to have various clinical comorbidities and had worse 1-year MACE outcomes compared with patients who reported low out-of-pocket costs. Regardless of self-reported out-of-pocket copay burden, patients who had a voucher for a P2Y12 inhibitor had significantly improved 1-year persistence to PY212 inhibitors compared with the group of patients who had self-reported copay costs from the same copay strata and no voucher. We did not find a larger impact for the copay intervention in patients with a higher copayment burden compared with those with a lower copayment burden.

Importantly, we found that regardless of the patient's self-reported total out-of-pocket costs, patients who had a voucher for a P2Y12 inhibitor had improved 1-year persistence after hospitalization for an MI. We hypothesized that the copay intervention would be associated with a greater increase in 1-year persistence of oral P2Y12 inhibitors among patients with higher copayment burden than those with lower copayment burden. While there was a significant increase in 1-year persistence for all groups with copayment offset (ie, voucher) regardless of self-reported out-of-pocket costs, there were no significant differences in the relative improvement in 1-year oral P2Y12 inhibitor persistence for patients in the high or middle copayment group without a voucher compared with patients in the low copayment group without a voucher.

Our findings are similar to those from the MI FREEE (Post-Myocardial Infarction Free Rx Event and Economic Evaluation) trial. In that trial, patients with a recent MI who were assigned to full prescription coverage of post-MI medications, including β-blockers, angiotensin-converting enzyme inhibitors, and statins had significantly improved medication adherence compared with those assigned to usual drug coverage.[8] Similar to our findings for 1-year persistence of P2Y12 inhibitors, the MI FREEE trial demonstrated that this benefit in adherence to post-MI medications was independent of baseline copayment levels. Because patients with higher copayment burden are less likely to be adherent to medications, we hypothesized that they may benefit more from the intervention in terms of improved persistence to oral P2Y12 inhibitors, but our findings did not support this hypothesis. Further work is needed to determine whether there are groups of patients based on other factors besides copayment burden that may differentially benefit from a copayment voucher. Ideally, future work would identify specific groups that could benefit the most from copayment vouchers.

Although we demonstrated a significant improvement in 1-year persistence across all copayment groups with a voucher compared with patients in the low copayment tier without a voucher, we did not

demonstrate a significant impact of the voucher and copayment levels on clinical outcomes. In fact, the group of patients with a high copay and a voucher had significantly higher rates of MACE compared with the low copay group without a voucher. Indeed, in the overall study population, the ARTEMIS trial did not demonstrate any significant difference in clinical outcomes between the intervention (voucher) group and the usual care arm.[12] Even in MI FREEE, where there were improvements in adherence to multiple guideline-recommended medications, there was no significant difference in the primary outcome, the first major cardiovascular event or revascularization, between the intervention and usual coverage arms.[8] As noted by Jackevicius and Ko,[13] though ARTEMIS demonstrated improvement in adherence rates to P2Y12 inhibitors in the intervention arm, the adherence rate in the intervention was still only 55%, a 9% increase from the usual care arm. Although this increase is significant, it was likely not large enough to impact clinical outcomes. Similarly, though we demonstrated increased persistence, there is not always a direct link between increased persistence and improved clinical outcomes. Given the indirect link between persistence and improved outcomes, most trials (including ARTEMIS) have been underpowered to detect differences in clinical outcomes. Moreover, improving clinical outcomes most likely requires a multipronged approach, including improved adherence, persistence, outpatient follow-up, health literacy, and ability to afford medications.

There are several important limitations of the current study. Although we adjusted for an extensive list of clinically relevant variables for the adjusted analyses (1-year persistence and 1-year clinical events), unmeasured confounders may still exist. We measured patient-reported persistence, as well as persistence validated through pharmacy fill data. However, we were not able to determine whether the patient was actually ingesting the medication. Additionally, it is possible that there were patients who used more than one pharmacy during the study period and that one of the pharmacies was not participating in the Symphony claims database. Furthermore, we based the copay groups on patient self-reported out-of-pocket costs. These groups may be subject to misclassification if patients underestimate or overestimate out-of-pocket costs. As previously described, only 72% of patients in the intervention (voucher) arm actually used the voucher.[12] Thus, there may have been a greater (or lesser) impact of the voucher across the various copayment tiers, if it were possible to account for this additional confounder. Finally, we are not able to determine the voucher's relationship to percentage of total drug costs, total healthcare spending, or disposable income.

CONCLUSIONS

Provision of copayment assistance was associated with higher medication persistence 1 year after MI regardless of out-of-pocket medication cost burden. As such, use of copayment vouchers should not necessarily be reserved for patients with high copayment burden. However, copayment assistance alone does not appear to improve post-MI clinical outcomes, even in patients with high copayment burden.

ARTICLE INFORMATION

Received April 9, 2022; accepted September 12, 2022.

Affiliations

Duke University School of Medicine, Durham, NC (J.A.R., T.Y.W.); Duke Clinical Research Institute, Durham, NC (J.A.R., L.A.K., T.Y.W.); University of Texas Southwestern Medical Center, Dallas, TX (E.D.P.); Cardiovascular Research Foundation, New York, NY (D.J.C.); St. Francis Hospital, Roslyn, NY (D.J.C.); University of California Los Angeles Medical Center, Los Angeles, CA (G.C.F.); Brigham and Women's Hospital, Boston, MA (N.K.C., C.P.C.); and The Christ Hospital, Cincinnati, OH (T.D.H.).

Disclosures

Dr Rymer reports research support from Boston Scientific and Abbott. Dr Peterson reports research support from Amgen, Janssen, Esperion, and BMS, and consults for Novo Nordisk, Janssen, Bayer, Pfizer, Livongo, and Cerner. Dr Cohen reports grant support from Edwards LifeSciences, Abbott, Boston Scientific, Medtronic, Daiichi-Sankyo, Brain-Q, Ther-Ox, Corvia, and V-Wave Medical, and consulting income from Edwards LifeSciences, Abbott, Boston Scientific, Medtronic, Impulse Dynamics, Bristol-Myers Squibb, and MyoKardia. Dr Fonarow consults for Abbott, Amgen, AstraZeneca, Bayer, Janssen, Medtronic, Merck, and Novartis. Dr Choudhry receives unrestricted grant support payable to his institution from Humana Inc., is a consultant for RxAnte and Decipher Health, and receives consulting fees from Veracity Healthcare Analytics. Dr Cannon reports receiving research grant support from Amgen, Arisaph, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Merck, and Takeda, and receiving consulting honoraria from Alnylam, Amarin, Amgen, Arisaph, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Janssen, Kowa, Lipimedix, Merck, Pfizer, Regeneron, Sanofi, and Takeda. Dr Henry reports receiving a steering committee honorarium for ARTEMIS from AstraZeneca. Dr Wang reports receiving research grant support to the Duke Clinical Research Institute from Amgen, AstraZeneca, Bristol-Myers Squibb, Cryolife, Novartis, Pfizer, Portola, and Regeneron, and receiving consulting honoraria from Grifols and Gilead. Ms Kaltenbach has no disclosures to report.

Acknowledgments

Drs Rymer and Wang, as well as Ms Kaltenbach, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Drs Rymer and Wnag; acquisition, analysis, or interpretation of data: all authors; drafting of the article: all authors; critical revision of the article for important intellectual content: all authors; statistical analysis: Drs Rymer and Wang and Ms Kaltenbach; obtained funding: Dr Wang; administrative, technical, or material support: Drs Wang and Rymer; supervision: all authors. Role of the funder/sponsor: funding for the study was provided by AstraZeneca. 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. AstraZeneca collaborated in the design of the study and reviewed and approved the article before submission of the article for publication. The final decision for article submission was made by the academic investigators; the sponsor did not have a right to veto such a decision.

Sources of Funding

This study was supported by a research grant from AstraZeneca to the Duke Clinical Research Institute.

Supplemental Material

Table S1

REFERENCES

1. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lane RA, Mack MJ, Mauri L, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation* 2016;134:e123-155, doi: 10.1161/CIR.0000000000000404.
2. Mathews R, Peterson ED, Honeycutt E, Chin CT, Effron MB, Zettler M, Fonarow GC, Henry TD, Wang TY. Early medication nonadherence after acute myocardial infarction: Insights into actionable opportunities from the TReatment with ADP receptor iNhibitorS: longitudinal assessment of treatment patterns and events after acute coronary syndrome (TRANSLATE-ACS) study. *Circ Cardiovasc Qual Outcomes*. 2015;8:347–356. doi: 10.1161/CIRCOUTCOMES.114.001223
3. 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. doi: 10.1016/j.ahj.2015.03.019
4. Doll JA, Hellkamp AS, Goyal A, Sutton NR, Peterson ED, Wang TY. Treatment, outcomes, and adherence to medication regimens among dual Medicare-Medicaid-eligible adults with myocardial infarction. *JAMA Cardiol*. 2016;1:787–794. doi: 10.1001/jamacardio.2016.2724
5. Mehran R, Baber U, 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. doi: 10.1016/S0140-6736(13)61720-1
6. Spertus JA, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, Messenger JC, Khanal S, Peterson ED, Bach RG, 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. doi: 10.1161/CIRCULATIONAHA.106.618066
7. 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. doi: 10.1016/j.ahj.2011.06.007
8. Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, Reisman L, Fernandes J, Spettell C, Lee JL, et al. Full coverage for preventive medications after myocardial infarction. *N Engl J Med*. 2011;365:2088–2097. doi: 10.1056/NEJMsa1107913
9. Trivedi AN, Moloo H, Mor V. Increased ambulatory care copayments and hospitalizations among the elderly. *N Engl J Med*. 2010;362:320–328. doi: 10.1056/NEJMsa0904533
10. Thornton Snider J, Seabury S, Lopez J, Mckenzie S, Goldman DP. Impact of type 2 diabetes medication cost sharing on patient outcomes and health plan costs. *Am J Manag Care*. 2016;22:433–440.
11. Karaca-Mandic P, Jena AB, Joyce GF, Goldman DP. Out-of-pocket medication costs and use of medications and health care services among children with asthma. *JAMA*. 2012;307:1284–1291. doi: 10.1001/jama.2012.340
12. Wang 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. doi: 10.1001/jama.2018.19791
13. Jackevicius CA, Ko DT. Medication co-payment vouchers, adherence with antiplatelet therapy, and adverse cardiovascular events after myocardial infarction. *JAMA*. 2019;321:37–39. doi: 10.1001/jama.2018.20396

SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics of the Final Study Population compared with the Excluded Study Population.

Variable	Study Population (N=7351)	Excluded Population (N=978)	p-value
Demographics			
Age, median (25th, 75th)	62 (54, 70)	60 (51, 69)	<0.0001
Female sex	2433 (33.1)	262 (26.8)	<0.0001
Hispanic	262 (3.6)	37 (3.8)	0.73
Black	748 (10.2)	90 (9.2)	0.34
Insurance payor			
Private	4667 (63.5)	657 (67.2)	0.02
Medicare	3223 (43.8)	340 (34.8)	<0.0001
Medicaid	660 (9.0)	82 (8.4)	0.54
Medical history			
Prior MI	1581 (21.5)	122 (12.5)	<0.0001
Prior PCI	1968 (26.8)	143 (14.6)	<0.0001
Prior CABG	862 (11.7)	61 (6.2)	<0.0001
Prior stroke/TIA	510 (6.9)	38 (3.9)	0.0003
PAD	477 (6.5)	41 (4.2)	0.0052
Heart failure	592 (8.1)	53 (5.4)	0.0038
Diabetes	2528 (34.4)	191 (19.5)	<0.0001
Hypertension	5296 (72.0)	439 (44.9)	<0.0001
Hyperlipidemia	4497 (61.2)	368 (37.6)	<0.0001
ESRD on dialysis	145 (2.0)	11 (1.1)	0.07
P2Y12 inhibitor use prior to admission	1128 (15.3)	74 (7.6)	<0.0001
In-hospital characteristics			
STEMI	3323 (45.2)	506 (51.7)	0.0001

Killip Class III/IV	233 (3.2)	22 (2.3)	0.18
Catherization performed	7217 (98.2)	956 (97.8)	0.36
PCI performed	6538 (88.9)	888 (90.8)	0.08
In-hospital events			
MACE	56 (0.76)	11 (1.1)	0.23
Bleeding event	136 (1.9)	13 (1.3)	0.25
Recurrent MI	36 (0.5)	9 (0.9)	0.08
Heart failure	398 (5.4)	50 (5.1)	0.69
Cardiac arrest	185 (2.5)	36 (3.7)	0.07
Stroke	0.3%	0.3%	0.03
Discharge P2Y12 inhibitor prescribed			0.10
Clopidogrel	3455 (47.0)	432 (44.2)	
Ticagrelor	3896 (53.0)	546 (55.8)	