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ORIGINAL RESEARCH

Association Between Copayment Amount and Filling of Medications for Angiotensin Receptor Neprilysin Inhibitors in Patients With Heart Failure

Amrita Mukhopadhyay, MD; Samrachana Adhikari, PhD; Xiyue Li, MS; John A. Dodson, MD, MPH; Ian M. Kronish, MD, MPH; Binita Shah, MD, MS; Maggie Ramatowski, BA; Rumi Chunara, PhD; Sam Kozloff, MD; Saul Blecker, MD

BACKGROUND: Angiotensin receptor neprilysin inhibitors (ARNI) reduce mortality and hospitalization for patients with heart failure. However, relatively high copayments for ARNI may contribute to suboptimal adherence, thus potentially limiting their benefits.

METHODS AND RESULTS: We conducted a retrospective cohort study within a large, multi-site health system. We included patients with: ARNI prescription between November 20, 2020 and June 30, 2021; diagnosis of heart failure or left ventricular ejection fraction ≤40%; and available pharmacy or pharmacy benefit manager copayment data. The primary exposure was copayment, categorized as $0, $0.01 to $10, $10.01 to $100, and >$100. The primary outcome was prescription fill nonadherence, defined as the proportion of days covered <80% over 6 months. We assessed the association between copayment and nonadherence using multivariable logistic regression, and nonbinarized proportion of days covered using multivariable Poisson regression, adjusting for demographic, clinical, and neighborhood-level covariates. A total of 921 patients met inclusion criteria, with 192 (20.8%) having $0 copayment, 228 (24.8%) with $0.01 to $10 copayment, 206 (22.4%) with $10.01 to $100, and 295 (32.0%) with >$100. Patients with higher copayments had higher rates of nonadherence, ranging from 17.2% for $0 copayment to 34.2% for copayment >$100 ($P$<0.001). After multivariable adjustment, odds of nonadherence were significantly higher for copayment of $10.01 to $100 (odds ratio [OR], 1.93 [95% CI, 1.15–3.27], P=0.01) or >$100 (OR, 2.58 [95% CI, 1.63–4.18], P<0.001), as compared with $0 copayment. Similar associations were seen when assessing proportion of days covered as a proportion.

CONCLUSIONS: We found higher rates of not filling ARNI prescriptions among patients with higher copayments, which persisted after multivariable adjustment. Our findings support future studies to assess whether reducing copayments can increase adherence to ARNI and improve outcomes for heart failure.

Key Words: angiotensin receptor-neprilysin inhibitor ■ copayment ■ heart failure ■ medication adherence ■ out-of-pocket cost ■ sacubitril-valsartan

Angiotensin receptor neprilysin inhibitors (ARNI) reduce mortality and hospitalization for patients with heart failure (HF).[1] However, poor adherence to filling ARNI prescriptions occurs in 40% to 80% of patients and is associated with increased hospitalization and death.[2,3] Relatively high copayment requirements for ARNI may contribute to this shortfall.[4–6] This is because there is currently only 1 Food and Drug Administration-approved ARNI (sacubitril-valsartan), and no generic version is currently available.[5]

Correspondence to: Amrita Mukhopadhyay, MD, Division of Cardiology, Department of Medicine, New York University School of Medicine, 227 East 30th Street, 8th Floor, New York, NY 10016. Email: amrita.mukhopadhyay@nyulangone.org

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CLINICAL PERSPECTIVE

What Is New?

- In this retrospective cohort study of patients with heart failure and angiotensin receptor neprilysin inhibitor prescription, higher copayment amount was associated with lower adherence to angiotensin receptor neprilysin inhibitors as measured by pharmacy fills.
- This association persisted after adjustment for demographic and clinical variables and was modified by neighborhood-level socioeconomic status.

What Are the Clinical Implications?

- Given marked reductions in hospitalization and mortality for patients with heart failure who use angiotensin receptor neprilysin inhibitors, our findings underscore the importance of addressing cost-related barriers for this life-saving therapy.
- Further research and interventions should be directed toward reducing or even eliminating copayments for angiotensin receptor neprilysin inhibitors, which could be cost saving overall, and assessing the effect of copayments on health inequities.

Nonstandard Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
ARNI	angiotensin receptor neprilysin inhibitors
ED	emergency department
PDC	Proportion of days covered

Prior studies have shown an association between higher copayments and lower medication adherence among patients with HF.[7–9] However, these studies relied primarily on claims data, which lack information on prescription time, and therefore cannot examine whether copayment amount is associated with primary nonadherence (also known as noninitiation of new prescriptions), nor account for periods of time when a prescription was held or stopped by a physician (also known as drug holidays).[10] Moreover, certain factors, such as income,[11] race,[12,13] and comorbidity burden,[14] are known to be associated with copayment-related nonadherence for other cardiovascular medications. For ARNI, the high cost[5] combined with the complex, multidrug regimen required for HF[15] may place certain subgroups at greater risk. For example, a recent study found that lower household income was associated with lower adherence to ARNI.[16] Such inequities could be exacerbated by copayments, and whether the association between copayment and adherence varies for certain subgroups is poorly understood.

In this context, we designed a study to retrospectively examine patients with HF seen at a large, racially diverse, urban, multipractice health system to assess whether there was an association between copayment amount and ARNI fill adherence. In order to overcome the limitations of prior analyses, which had used claims data, we created a data set that combined prescribing information from the electronic health records with medication fill information from pharmacies. This enabled us to more accurately understand the association between copayment amount and ARNI fill adherence as well as to conduct separate analyses examining whether copayment amount was associated with noninitiation of ARNI in patients newly prescribed this class of medication.

METHODS

Study Design, Setting, and Participants

The data that support the findings of this study are available from the corresponding author upon reasonable request. We conducted a retrospective cohort study of patients with HF at a large, multipractice health system (New York University Langone Health). Data were obtained from the electronic health record (Epic, Epic Systems, Verona, WI), which was linked to pharmacy data on medication fills and copayment amounts via Surescripts (Surescripts, LLC, Arlington, VA). We included patients over 18 years of age with the following: a diagnosis of HF listed in the problem list, visit diagnosis, or billing code (see Data S1 for *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes selected using methodology from the Center for Medicare & Medicaid Services[17]), or a left ventricular ejection fraction (LVEF) ≤40% on echocardiogram; prescription for ARNI between November 20, 2020 and June 30, 2021; and available copayment data. Patients were followed for 6 months through December 31, 2021. These dates were chosen because of the availability of copayment and prescription fill data in our data set. This study was approved by the New York University Institutional Review Board with a waiver of informed consent.

Outcome Measures

Our primary outcome of interest was ARNI fill nonadherence over the course of 6 months from time of prescription. We measured medication fill adherence using the proportion of days covered (PDC) metric recommended by the National Quality Forum and Pharmacy Quality Alliance.[18] PDC was defined by the ratio of the number of days of dispensed medications

filled at the pharmacy to the number of days with an active prescription, with higher ratios indicating better adherence. If there was a lapse in prescription, the number of days with no prescription was excluded from the denominator, as previously described.[10] We combined 2 data sources to calculate PDC: (1) pharmacy fill information obtained through Surescripts, and (2) prescription information obtained through the electronic health record. By linking electronic health record prescribing information, our PDC calculation accounted for prescriptions that were never filled, discontinuation of prescriptions by the provider, and periods of time where prescription had lapsed. PDC was measured for 6 months following prescription initiation or renewal. We assessed PDC as a binary variable to classify patients' adherence status: PDC <0.8 (nonadherent) and PDC ≥0.8 (adherent). This classification of PDC to define nonadherence is widely used in the literature and has previously been associated with outcomes in HF.[2,19]

We also assessed 2 secondary outcomes: (1) ARNI fill adherence as measured by PDC as a continuous variable and (2) ARNI initiation, defined as filling ARNI prescription within 6 months of being prescribed ARNI for the first time, using a look-back period to January 1, 2015 to ensure no prior prescriptions for ARNI.

Covariables of Interest

Copayment

Information regarding copayment amount in US dollars was gathered at the time of prescription using the Real-Time Prescription Benefit service (Surescripts, LLC),[20] which sources data from pharmacy benefit managers and health plans and was linked to the electronic health record. Copayment amount for the incident prescription order was assessed as a continuous variable and was further categorized into the following 4 prespecified groups based on sample distribution to allow for adequate sample size in each category and also rounded to account for possible psychological impacts of price[21]: $0, $0.01 to $10, $10.01 to $100, and >$100.

Baseline Characteristics and Other Covariates

We extracted the following patient demographics from electronic health record data: age, sex, race, ethnicity, and insurance status. We categorized race as Asian, Black, White, and other (includes American Indian, Alaskan Native, Native Hawaiian, or Other Pacific Islander), and ethnicity as Hispanic/Latinx or Non-Hispanic/Latinx based on self-report. We categorized insurance status as Medicare (including managed Medicare), Medicaid (including managed Medicaid), Private (including preferred provider organization, exclusive provider organization, health maintenance organization, point of service, indemnity, and managed care), and other (including no fault and workers comp).

To account for illness severity, the following clinical covariates were also obtained at the time of prescription: most recent LVEF, any hospitalization in the prior year, any emergency department (ED) visits in the prior year, and comorbidity burden using Charlson comorbidity index.[22] LVEF was categorized in the following groups: <25%, 26% to 35%, 36% to 40%, and >40%. Charlson comorbidity index score was computed using comorbidities listed in the electronic health record problem list at the time of prescription.

To obtain neighborhood-level socioeconomic status, we identified the corresponding census tract for each patient by geocoding their home address at time of prescription using DeGAUSS geocoding tool.[23] Census tracts are geographical units with populations of ≈4000 people. We subsequently linked each patient to census tract-level data from the US Census Bureau's American Community Survey,[24] a rolling survey of the US population. Variables from the survey were then used to compute the Agency for Healthcare Research and Quality (AHRQ) Socioeconomic Status (SES) index score,[25] a geographical area-based measure of socioeconomic status by neighborhood that combines information on number of people living per room, property value, unemployment, percentage living below poverty level, household income, and education. Higher scores correspond to higher neighborhood socioeconomic status.

Statistical Analysis

Baseline characteristics (age, sex, race, ethnicity, insurance status, SES index, LVEF, hospitalization in the past year, ED visit in the past year, and comorbidity burden) were tabulated for all patients and by categories of copayment amount for ARNI. Unadjusted differences in baseline characteristics and outcomes by copayment amount were assessed using chi-square tests for proportions or ANOVA as appropriate.

Multivariable logistic regression was used to assess the association between categories of copayment amount and primary outcome of adherence status (PDC<0.8: nonadherence), adjusting for the following prespecified covariates chosen based on prior literature[11–14]: age, sex, race, ethnicity, insurance type, ED visit in the past year, hospitalization in the past year, LVEF, Charlson comorbidity index score, and AHRQ SES index score. We included a separate missingness category for race, ethnicity, LVEF, and SES index score in fully adjusted models to avoid systematic exclusion of patients with missing data. Patients with missing insurance status (n=3) were excluded from fully adjusted models. Although the model with categorical

copayment was considered as the primary approach for interpretability, to visualize the potential nonlinear association between nonadherence (PDC<0.8) and continuous copayment exposure, restricted cubic spline with 5 knots was specified for copayment in the logistic regression model. Plots with model-predicted probabilities of nonadherence at each level of copayment compared with the predicted probability at no copayment, along with 95% CI, were generated. In another secondary analysis, Poisson regression with robust standard error accounting for underdispersion was used to assess the association between copayment amount and continuous PDC, which was computed as a proportion, adjusting for the same covariates. This was done to supplement the primary logistic regression analysis to allow for assessment of PDC as a continuous outcome and also because the relatively high prevalence of nonadherence in our sample may give the appearance of inflated risk when using odds ratios (ORs) as opposed to relative risk. Denominator of the PDC was specified as offset term in the Poisson regression. Poisson regression was chosen for this analysis because PDC is a proportion with nonnormal distribution.[26] ORs and 95% CIs were reported for binary outcomes, whereas incidence rate ratios and 95% CIs were reported for the rate outcomes. Adjusted analysis was not conducted for the secondary outcome of ARNI initiation owing to limitations in power, as only 44% of patients in the sample were being prescribed ARNI for the first time.

To assess for moderators of copayment-related nonadherence, separate stratified analyses were conducted for the following prespecified subgroups: age (above versus below median), sex (female versus male), race (Black versus White), and AHRQ SES index score (above versus below median). For each subgroup, logistic regression was used to assess the association between copayment amount and the primary outcome of fill nonadherence (PDC<0.8), adjusting for the following covariates (except for the stratified group): age, sex, race, ethnicity, insurance type, ED visit in the past year, hospitalization in the past year, LVEF, Charlson comorbidity index score, and AHRQ SES index score. Likelihood ratio test was used to assess goodness of fit of adjusted models with and without interaction for each moderator. Significance level was set at a 2-sided alpha level of 0.05. Statistical analyses were performed using R Statistical Software (v4.0.4; R Core Team 2021).

RESULTS

Sample Characteristics

Figure 1 depicts cohort assembly. Among 2956 patients meeting other eligibility criteria, 921 (31%) patients had available copayment data. Slightly under half (44%, n=406) were being prescribed ARNI for the first time. Average time since diagnosis was 2 years (range: 0–11.4 years). Copayment amount for incident prescription order ranged from $0 to $3156.64, with 192 (20.8%) patients having no copayment, 228 (24.8%) patients having copayment $0.01 to $10, 206 (22.4%) with copayment $10.01 to $100, and 295 (32.0%) with copayment over $100. The incident prescription order duration was 30 days or 90 days for the majority of patients (93.2%). The majority (85.8%, n=790) of patients had active ARNI prescription during the entire 6-month follow-up period (median duration of active prescription: 180 days, range: 2–180 days). Characteristics of prescription duration, stoppage, and interruption are provided in Table S1.

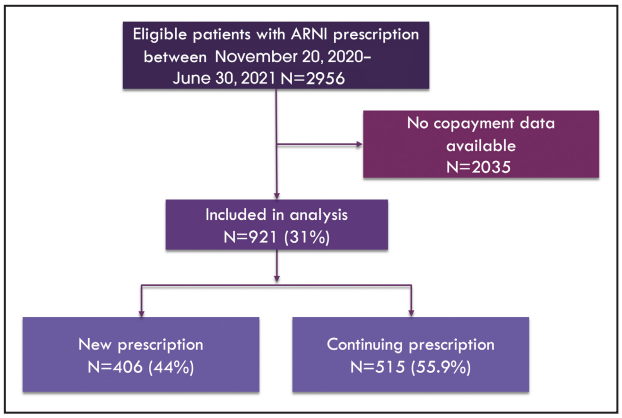

Figure 1. Cohort assembly.
ARNI indicates angiotensin receptor neprilysin inhibitor.

As seen in Table 1, copayment amount varied significantly by baseline demographic and clinical characteristics. The majority of patients with Medicaid insurance had copayments of $0.01 to $10 (125/132, 94.7%), whereas more variation in copayment amount was observed for patients with Medicare and commercial insurance. Patients with no copayment tended to be female, have higher Charlson comorbidity index scores, and live in neighborhoods with below median AHRQ SES index score. Patients with copayment over $100 tended to be White race, Non-Hispanic/Latinx ethnicity, have LVEF >35%, and live in neighborhoods above median AHRQ SES index score. Patients who were Black race, Hispanic/Latinx ethnicity, or had ED visit in the past year tended to have copayments of $0.01 to $10. Older patients tended to be more likely to either have no copayment or copayment over $100.

Association Between Copayment Amount and ARNI Fill Adherence

The percentage of patients with ARNI fill nonadherence, defined as PDC<0.8, varied significantly by copayment amount (P<0.001, Table 2). Patients with no copayment included a smaller proportion of patients

Table 1. Baseline Characteristics by Copayment Amount. Other race category included: American Indian, Alaskan Native, Native Hawaiian, or Other Pacific Islander based on self-report

		Copayment amount				
	Total sample	$0	$0.01–10	$10.01–100	$100+	
	N=921	N=192 (20.8%)	N=228 (24.8%)	N=206 (22.4%)	N=295 (32.0%)	*P* value*
Age, y, mean (SD, range)	68.55 (13.67, 28–100)	71.69 (13.51, 32–100)	62.07 (13.22, 28–95)	67.54 (12.50, 29–95)	72.21 (13.00, 31–100)	*P*<0.001*
Sex, female (%)	269 (29.2%)	70 (36.5%)	69 (30.3%)	44 (21.4%)	86 (29.2%)	*P*=0.01
Race, N (%)						*P*<0.001
White	558 (60.6%)	106 (55.2%)	107 (46.9%)	134 (65.0%)	211 (71.5%)	
Black	151 (16.4%)	33 (17.2%)	50 (21.9%)	30 (14.6%)	38 (12.9%)	
Other	111 (12.1%)	23 (12.0%)	43 (18.9%)	26 (12.6%)	19 (6.4%)	
Asian	48 (5.2%)	15 (7.8%)	16 (7.0%)	8 (3.9%)	9 (3.1%)	
Refused/unknown	49 (5.3%)	13 (6.8%)	11 (4.8%)	7 (3.4%)	18 (6.1%)	
Missing	4 (0.4%)	2 (1.0%)	1 (0.4%)	1 (0.5%)	0 (0.0%)	
Ethnicity, N (%)						*P*<0.001
Hispanic/Latino	126 (13.7%)	24 (12.5%)	55 (24.1%)	25 (12.1%)	22 (7.5%)	
Non-Hispanic/Latino	695 (75.5%)	144 (75.0%)	158 (69.3%)	165 (80.1%)	228 (77.3%)	
Refused/unknown	94 (10.2%)	22 (11.5%)	13 (5.7%)	15 (7.3%)	44 (14.9%)	
Missing	6 (0.7%)	2 (1.0%)	2 (0.9%)	1 (0.5%)	1 (0.3%)	
Insurance, N (%)						*P*<0.001
Medicare	520 (56.5%)	137 (71.4%)	89 (39.0%)	87 (42.2%)	207 (70.2%)	
Commercial	266 (28.9%)	52 (27.1%)	14 (6.1%)	115 (55.8%)	85 (28.8%)	
Medicaid	132 (14.3%)	3 (1.6%)	125 (54.8%)	2 (1.0%)	2 (0.7%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Missing	3 (0.3%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	1 (0.3%)	
Ejection fraction, N (%)						*P*=0.01
<25%	136 (14.8%)	30 (15.6%)	44 (19.3%)	26 (12.6%)	36 (12.2%)	
25%–35%	298 (32.4%)	57 (29.7%)	76 (33.3%)	82 (39.8%)	83 (28.1%)	
35%–40%	124 (13.5%)	26 (13.5%)	21 (9.2%)	26 (12.6%)	51 (17.3%)	
40%+	202 (21.9%)	37 (19.3%)	45 (19.7%)	42 (20.4%)	78 (26.4%)	
Missing	161 (17.5%)	42 (21.9%)	42 (18.4%)	30 (14.6%)	47 (15.9%)	
Emergency department visit in past year, N (%)	76 (8.3%)	6 (3.1%)	28 (12.3%)	17 (8.3%)	25 (8.5%)	*P*=0.009
Hospitalization in past year, N (%)	210 (22.8%)	36 (18.8%)	56 (24.6%)	45 (21.8%)	73 (24.7%)	*P*=0.40

(*Continued*)

Table 1. Continued

	Total sample	Copayment amount				
		$0	$0.01–10	$10.01–100	$100+	
	N=921	N=192 (20.8%)	N=228 (24.8%)	N=206 (22.4%)	N=295 (32.0%)	*P* value*
Charlson comorbidity index score, mean (SD, range)	3.04 (2.37, 0–15)	3.54 (2.60, 0–15)	2.93 (2.32, 0–13)	2.68 (1.99, 0–11)	3.06 (2.45, 0–13)	*P*=0.003†
Agency for Healthcare Research and Quality Socioeconomic Status index score, N (%)						*P*<0.001
Quartile 1 (<54.75)	200 (21.7%)	60 (31.2%)	70 (30.7%)	25 (12.1%)	45 (15.3%)	
Quartile 2 (54.75–55.84)	199 (21.6%)	54 (28.1%)	49 (21.5%)	50 (24.3%)	46 (15.6%)	
Quartile 3 (55.84–57.27)	201 (21.8%)	31 (16.1%)	56 (24.6%)	41 (19.9%)	73 (24.7%)	
Quartile 4 (57.27+)	200 (21.7%)	32 (16.7%)	27 (11.8%)	55 (26.7%)	86 (29.2%)	
Missing	121 (13.1%)	15 (7.8%)	26 (11.4%)	35 (17.0%)	45 (15.3%)	

*P value from Pearson's chi-square test unless otherwise indicated.
† P value from ANOVA test.

who were nonadherent (17.2%), as compared with patients with copayment of $0.01 to $10 (28.9%), $10.01 to $100 (27.2%), or over $100 (34.2%). ARNI fill adherence as per PDC, a continuous outcome, also varied significantly by copayment amount (*P*<0.001). Mean PDC was higher for patients with no copayment (0.89 ± 0.23) as compared with patients with copayment of $0.01 to $10 (0.83 ± 0.27), $10.01 to $100 (0.83 ± 0.29), or over $100 (0.77 ± 0.34). For patients being prescribed ARNI for the first time, rates of initiation also varied significantly by copayment amount (*P*=0.047). Among patients newly prescribed ARNI, a greater proportion of patients with no copayment initiated ARNI within 6 months (97.4%), as compared with patients with copayment of $0.01 to $10 (95.4%), $10.01 to $100 (92.2%), or over $100 (87.9%).

Figure 2 depicts results of multivariable logistic regression to assess the odds of ARNI nonadherence by copayment amount. In unadjusted analysis, odds of ARNI fill nonadherence (PDC<0.8) was significantly higher for patients with all categories of copayment amounts as compared with no copayment ($0.01–$10: OR, 1.96 [95% CI, 1.23–3.17], *P*<0.01; $10.01–$100: OR, 1.80 [95% CI, 1.11–2.94], *P*=0.02; $100+: OR, 2.51 [95% CI, 1.62–3.96], *P*<0.001). After adjustment for demographic and clinical covariates, there was a graded association between higher copayment amounts and increased odds of nonadherence. This increase in odds of nonadherence was statistically significant for patients with copayment of $10.01 to $100 (OR, 1.93 [95% CI, 1.15–3.27], *P*=0.01) and copayment over $100 (OR, 2.58 [95% CI, 1.63–4.18], *P*<0.001), as compared with patients with no copayment. For patients with copayment of $0.01 to $10, higher odds of nonadherence were also observed, but this was not statistically significant (OR, 1.40 [95% CI, 0.77–2.53], *P*=0.27).

Figure 3 depicts results of logistic regression models with cubic spline to assess relative risks of ARNI nonadherence by copayment amount as a continuous variable. In unadjusted analysis, relative risk of nonadherence increased as copayment increased, except at very high copayment amounts (>$500). This relationship was nonlinear, with greater increases in nonadherence at lower copayment amounts. In adjusted analysis, relative risk of nonadherence was higher for higher copayments for all copayment amounts, even those with very high copayments. This relationship was also nonlinear, with greater increases in nonadherence at lower copayment amounts.

A similar, graded association was observed between copayment amount and adherence measured by PDC as a continuous variable, with statistically significant differences observed for the higher copayment categories. In unadjusted models, PDC was significantly lower for patients with copayment of $10.01 to $100 (incidence rate ratio, 0.93 [95% CI, 0.86–0.996], *P*=0.04) and over

Table 2. Unadjusted Results for Primary and Secondary Outcomes by Copayment Amount

	Total	ARNI copayment amount				
	N=921	$0 N=192 (20.8%)	$0.01–10 N=228 (24.8%)	$10.01–100 N=206 (22.4%)	$100+ N=295 (32.0%)	*P* value
Primary outcome						
Patients nonadherent to ARNI (PDC<0.8), N (%)	256 (27.8%)	33 (17.2%)	66 (28.9%)	56 (27.2%)	101 (34.2%)	*P*<0.001
Secondary outcomes						
Adherence (PDC, continuous outcome), Mean (SD, range)	0.82 (0.29, 0–1)	0.89 (0.23, 0–1)	0.83 (0.27, 0–1)	0.83 (0.29, 0–1)	0.77 (0.34, 0–1)	*P*<0.001
Initiation (new prescription filled), N (%) N=406	375 (92.4%)	75 (97.4%) N=77	83 (95.4%) N=87	94 (92.2%) N=102	123 (87.9%) N=140	*P*=0.047

ARNI indicates angiotensin receptor neprilysin inhibitor; and PDC, proportion of days covered.

$100 (incidence rate ratio, 0.91 [95% CI, 0.84–0.98], *P*=0.01), as compared with patients with no copayment (Table S2). In adjusted models, PDC was significantly lower for patients with copayment over $100 as compared with patients with no copayment (incidence rate ratio, 0.90 [95% CI, 0.83–0.98], *P*=0.01).

Subgroup Analysis

In subgroup analysis, we found no significant effect of age, sex, or race on the relationship between copayment amount and medication adherence (*P*>0.10 for all interaction terms, Table 3). Neighborhood-level AHRQ SES index score significantly modified the relationship between copayment amount and medication fill adherence, such that this association was more pronounced for patients living in higher AHRQ SES index neighborhoods (*P*-interaction=0.007). Patients living in neighborhoods with above median AHRQ SES index scores had significantly higher odds of nonadherence when faced with any copayment amount, as compared with no copayment ($0.01–$10: OR, 3.46 [95% CI,

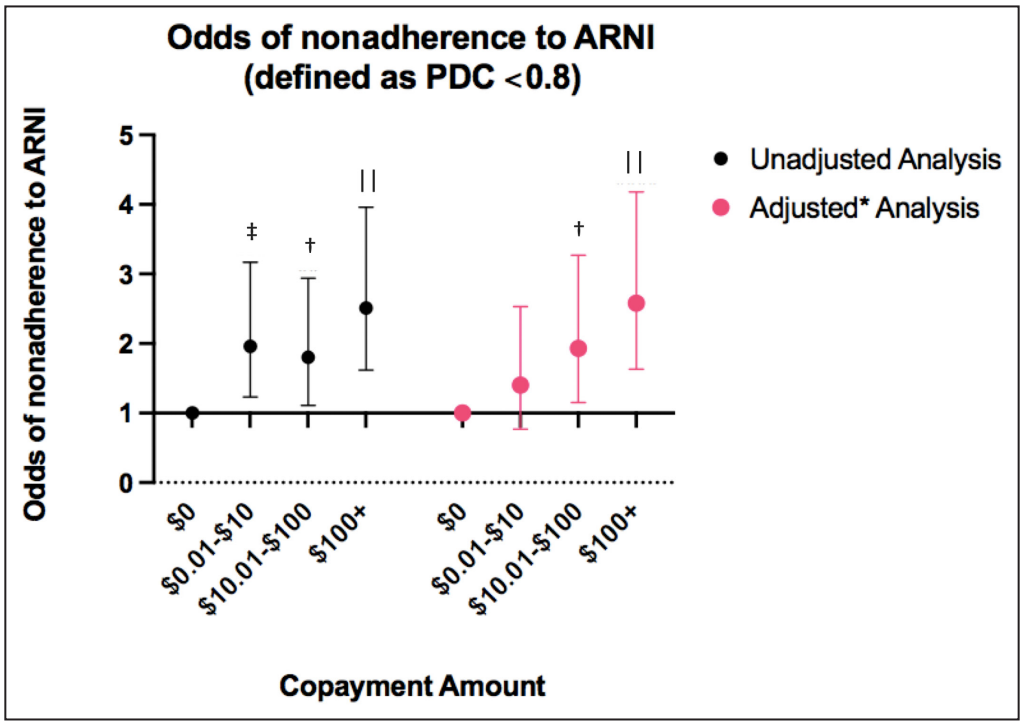

Figure 2. Odds of ARNI nonadherence (defined as PDC<0.8) by copayment amount.
*Adjusted for age, sex, race, ethnicity, insurance type, emergency department visit, hospitalization, Charlson comorbidity index score, LVEF, and AHRQ socioeconomic status index score. †*P*<0.05; ‡*P*<0.01; ‖*P*<0.001. AHRQ indicates Agency for Healthcare Research and Quality; ARNI, angiotensin receptor neprilysin inhibitor; LVEF, left ventricular ejection fraction; and PDC, proportion of days covered.

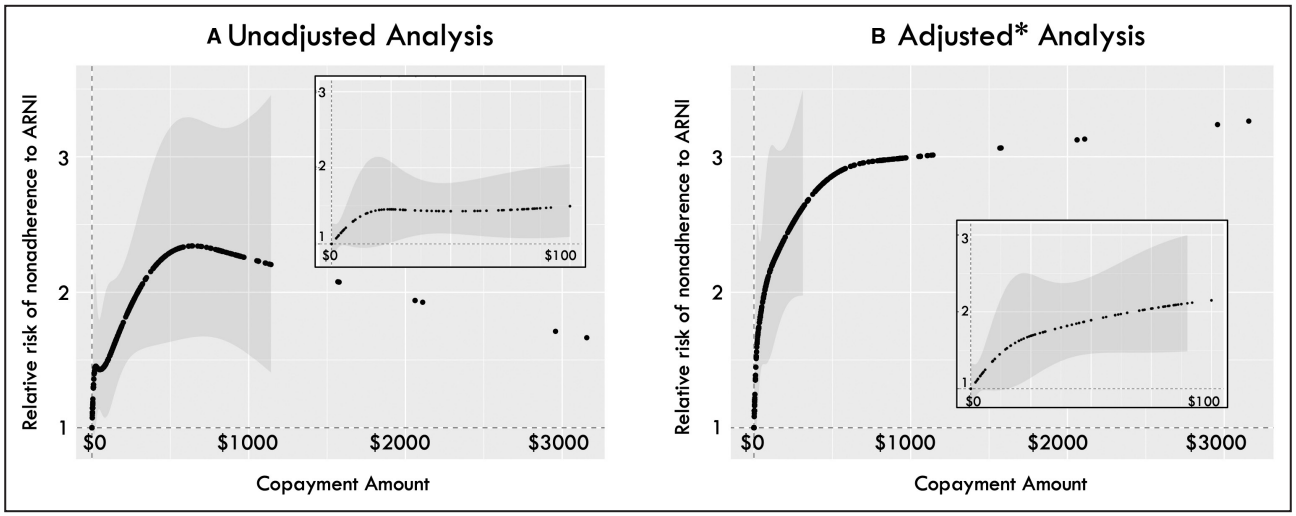

Figure 3. Relative risk of nonadherence to ARNI (defined as PDC<0.8) by copayment amount as a continuous variable. A, Unadjusted, and B, Adjusted* analysis using logistic regression with cubic spline.
*Adjusted for age, sex, race, ethnicity, insurance type, emergency department visit, hospitalization, Charlson comorbidity index score, LVEF, and AHRQ socioeconomic status index score. AHRQ indicates Agency for Healthcare Research and Quality; ARNI, angiotensin receptor neprilysin inhibitor; LVEF, left ventricular ejection fraction; and PDC, proportion of days covered.

1.11–12.21], *P*=0.04; $10.01–$100: OR, 6.52 [95% CI, 2.45–20.93], *P*<0.001; $100+: OR, 5.81 [95% CI, 2.30–18.00], *P*<0.001). In contrast, patients living in neighborhoods with below median AHRQ SES index scores had no significant difference in odds of nonadherence when comparing no copayment to copayment of $0.01 to $10 (OR, 0.84 [95% CI, 0.36–1.89], *P*=0.67) or $10.01 to $100 (OR, 0.82 [95% CI, 0.37–1.79], *P*=0.63) but did have increased odds of nonadherence for patients with copayment >$100 (OR, 1.97 [95% CI, 1.01–3.87], *P*=0.047). Absolute rates of nonadherence stratified by neighborhood AHRQ SES index score also revealed similar results. Among patients living in above median AHRQ SES index neighborhoods, there was a greater proportion of patients who were nonadherent for higher copayment amounts ($0: 7.9%, $0.01–$10: 26.8%, $10.01–$100: 31.3%, $100+ 32.1%). On the other hand, among patients living in below median AHRQ SES index neighborhoods, the proportion of patients who were nonadherent was more similar between different copayment amounts ($0: 22.8%, $0.01–$10: 27.5%, $10.01–$100: 21.3%, $100+: 33.0%).

DISCUSSION

In this retrospective cohort study of patients with HF and ARNI prescription, higher copayment amount was associated with lower adherence to ARNI as measured by pharmacy fills. This association persisted after adjustment for demographic and clinical variables and was modified by neighborhood-level socioeconomic status.

Suboptimal adherence to ARNI is common and is associated with increased hospitalization and death.[2] Our findings inform the hypothesis that high copayments could substantially contribute to these observed low rates of adherence, underscoring the importance of addressing cost-related barriers to therapy. In our cohort, >30% of patients had copayments >$100, which was associated with more than twice the odds of being nonadherent. Our results are consistent with prior literature on older classes of HF medications,[7–9] which also found an association between increased copayment and decreased medication fill adherence. One prior study using commercial insurance claims data examined multiple variables associated with ARNI adherence and did not find out-of-pocket cost to be independently associated with adherence.[6] We expand on this prior work by being able to include new and existing prescriptions, account for lapses in prescription, and include patients with a variety of insurance types.

Copayments are intended to reduce high cost use and are designed to encourage either use of a lower cost alternative, or to discontinue unnecessary therapy.[27] However, ARNI is a new medication in its class with no generic alternative and is recommended as class I in guidelines for most patients with HF and reduced LVEF.[28] Moreover, ARNI is actually underprescribed, with >80% of eligible HF patients not receiving a prescription, leading to an estimated 28 484 deaths per year nationwide.[29,30] Therefore, for ARNI, copayments may not actually reduce total costs and likely cause harm by affecting patient adherence to proven therapy, leading to increased morbidity, mortality, and overall rise in health care expenditures.

Table 3. Adjusted Odds of ARNI Fill Nonadherence (PDC<0.8) by Copayment Amount for Prespecified Subgroups

Characteristic	ARNI copayment	Number of patients	Adjusted odds ratio* (95% CI)	*P* value of interaction†
Age				*P*=0.11
Below median	0	74	1	
	0.01–10	168	1.65 (0.69–4.04)	
	10.01–100	114	1.33 (0.64–2.84)	
	100+	95	1.25 (0.58–2.76)	
Above median	0	118	1	
	0.01–10	60	1.22 (0.48–2.99)	
	10.01–100	92	2.46 (1.16–5.32)	
	100+	200	3.71 (1.97–7.29)	
Sex				*P*=0.78
Female	0	70	1	
	0.01–10	69	2.67 (0.85–8.56)	
	10.01–100	44	3.69 (1.20–11.84)	
	100+	86	4.46 (1.75–12.40)	
Male	0	122	1	
	0.01–10	159	1.17 (0.56–2.43)	
	10.01–100	162	1.58 (0.87–2.93)	
	100+	209	2.14 (1.23–3.81)	
Race				*P*=0.64
White	0	106	1	
	0.01–10	107	2.11 (0.88–5.11)	
	10.01–100	134	2.10 (1.01–4.54)	
	100+	211	3.06 (1.59–6.27)	
Black	0	33	1	
	0.01–10	50	1.76 (0.41–7.71)	
	10.01–100	30	1.13 (0.30–4.25)	
	100+	38	1.64 (0.48–5.80)	
SES index score				*P*=0.007
Below median	0	114	1	
	0.01–10	120	0.84 (0.36–1.89)	
	10.01–100	75	0.82 (0.37–1.79)	
	100+	91	1.97 (1.01–3.87)	
Above median	0	63	1	
	0.01–10	82	3.46 (1.11–12.21)	
	10.01–100	96	6.52 (2.45–20.93)	
	100+	159	5.81 (2.30–18.00)	

ARNI indicates angiotensin receptor neprilysin inhibitor; ED, emergency department; OR, odds ratio; and SES, socioeconomic status.

*Adjusted for age, sex, race, ethnicity, insurance, emergency department visit or hospitalization in the past year, ejection fraction, Charlson comorbidity index score, and SES index score (except for the stratified group).

†*P* value of ANOVA test between adjusted model with and without interaction.

Intervening on high copayments has proven complex and difficult. Some have suggested improved communication with patients regarding copayment-related barriers to facilitate education and shared decision-making.[31] However, copayment amount is often unknown until after the patient leaves the clinician's office. In our sample, we observed a wide range of copayments for various insurance types, ranging from $0 to $3156.64, highlighting a need for transparency in copayment amounts on an individual level to allow for such conversations to take place. Another potential solution includes providing vouchers or coupons to reduce financial burden for patients. One randomized study found improved fill adherence after providing patients with vouchers for antiplatelet agents after myocardial infarction.[32] However, over a quarter of patients did not use the voucher, and often these were patients with the greatest risk for adverse outcomes.

Reducing or eliminating copayments at the insurance level has the advantage of not placing the burden on the patient to remember to bring a voucher to the pharmacy, and it has also shown significant improvements in adherence in multiple studies,[13,33,34] including 1 randomized trial that eliminated copayments for preventative medications post-myocardial infarction, resulting in both improved adherence and reduced disparities in adherence.[12,35] However, these programs are usually feasible only within a single insurance plan and therefore benefit only a specific population. Moreover, they often target only 1 or a few medications, and may not account for poly-pharmacy or copayments from other medications. This is because copayment amounts are determined through complex negotiations between pharmacy benefit managers, insurers, pharmaceutical companies, and pharmacies. Therefore, government policies, such as global caps on copayment amounts, or even elimination of copayments for ARNI, should also be considered and studied. Notably, we found a graded association between copayment and ARNI adherence that was more pronounced at lower copayment amounts, suggesting that even modest copayments can affect adherence.

In addition to reduced adherence, copayments also have the potential to worsen inequities in care. Prior studies have found that high copayments differentially affect patients with lower income[11,12,36,37] and that patients with lower income are less likely to fill prescriptions for ARNI.[16] In our sample, we expected patients living in neighborhoods with low SES index to have greater risk of copayment-related decreases in adherence. However, we found the opposite interaction, where patients living in high SES index neighborhoods were actually more likely to be nonadherent when faced with high copayments as compared with patients living in low SES index neighborhoods, who had more similar rates of nonadherence for all copayment groups. This finding could be because of the presence of multiple components used to calculate the neighborhood SES index, such as income and education, which may differentially affect cost-related barriers to adherence. Additionally, neighborhood-level SES index may fail to capture important individual-level SES variables that affect adherence. Unfortunately, our data set did not contain reliable information regarding individual-level social determinants. Future studies with larger sample sizes are needed to better understand how different dimensions of SES influence the association between copayment amount and medication adherence.

Our results should be interpreted in the context of several limitations. First, this was a retrospective cohort study and is therefore limited in its ability to draw causal conclusions. Second, data were obtained from a single health system in New York City and therefore may be limited in generalizability. Third, data on copayment amount were not available for all patients, and systematic differences may exist for those patients excluded owing to unavailable data. Fourth, we did not account for complexity and cost for full medication regimen, but this may have been partly captured by indicators of comorbidity. We also did not have data on coupons, free samples, or other patient assistance programs, which may affect total out-of-pocket costs. Additionally, we could not assess whether patients were subject to copayment policies that relied on prior expenditures, such as with Medicare coverage gaps or other similar payment structures. Fifth, we included patients regardless of ejection fraction on echocardiogram because patients may have had recovery of ejection fraction, many had missing ejection fraction data, and ARNI was only indicated for HF with reduced ejection fraction per guidelines at the time of the study.[28] However, it is possible that some patients were included without a history of HF with reduced ejection fraction. We also included patients regardless of timing of HF diagnosis, and including both incident and prevalent HF may lead to some bias. Sixth, copayment amount for incident prescription order was used as the primary exposure to account for the payment required at the time a patient makes the decision to fill a prescription. However, some patients may make decisions based on cost-per-pill or cost-per-day. Finally, PDC assessed only whether a patient filled a medication at the pharmacy over a 6-month period and did not directly assess whether a medication was taken consistently, correctly, or for longer duration.

Strengths of this study include use of data from a racially diverse cohort of patients with different types of insurance plans. Additionally, we did not use claims data, but rather, combined prescribing data from electronic health records with medication fill data from pharmacies. This novel approach allowed for our measures of adherence to account for prescriptions that were never filled, discontinuation of prescriptions by the provider, and for periods of time where prescription had lapsed. Finally, although this was a single health system, New York University Langone Health has over 350 affiliated sites, ranging from community practice to tertiary care centers.

CONCLUSIONS

In conclusion, we found lower rates of ARNI adherence for patients with higher copayment amount. This persisted after multivariable adjustment of important demographic, clinical, and neighborhood-level variables. Given marked reductions in hospitalization and mortality for patients who use ARNI, our findings underscore the importance of addressing cost-related barriers for this therapy. Further research and interventions should

be directed toward increasing transparency regarding copayment, reducing or even eliminating copayments for ARNI, which could be cost saving overall, and assessing the effect of copayments on health inequities.

ARTICLE INFORMATION

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Affiliations

Department of Medicine (Cardiology) (A.M., J.A.D.); and Department of Population Health (S.A., X.L., M.R., S.B.), New York University School of Medicine, New York, NY; Center for Behavioral Cardiovascular Health, Columbia University Irving Medical Center, New York, NY (I.M.K.); Department of Medicine (Cardiology), VA New York Harbor Healthcare System, New York, NY (B.S.); Department of Medicine, University of Utah, Salt Lake City, NY (S.K.); New York University School of Computer Science & Engineering and School of Global Public Health, New York, NY (R.C.); and Department of Medicine, New York University School of Medicine, New York, NY (S.B.).

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Disclosures

Dr Shah serves on advisory boards for Philips Volcano and Horizon Therapeutics and is a consultant for Terumo Medical. The other authors have no disclosures to report.

Supplemental Material

Data S1
Tables S1–S2

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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

ICD-10 diagnoses codes for inclusion into the study, selected using methodology from Center for Medicare & Medicaid Services.[17]

1. I50.x Heart Failure
2. I11.0 Hypertensive heart disease with heart failure
3. I13.0 Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease
4. I13.2 Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end stage renal disease

Table S1. Characteristics of prescription duration, stoppage, and interruption

	Total sample N=921
Patients with prescription for full 6 months, N (%)	790 (85.8%)
Overall prescription duration (days), Median (IQR, range)	180 days (IQR = 0, range = 2-180)
Patients with prescription stopped and not re-started, N (%)	92 (9.9%)
Patients with interruption in prescription (stopped and re-started), N (%)	39 (4.2%)
Duration of prescription interruption (days), Median (IQR, range)	12 days (IQR = 26.5, range = 2-118)

IQR – interquartile range

Table S2. Adjusted and unadjusted incident rate ratios for PDC as a continuous outcome by copayment amount

Incident rate ratio (IRR) of adherence (PDC) for ARNI – IRR (95% CI)*	**ARNI Copayment Amount**			
	$0	$0.01-10	$10.01-100	$100+
	N=192 (20.8%)	N=228 (24.8%)	N=206 (22.4%)	N=295 (32.0%)
Unadjusted incident rate ratio	1.00	0.94 (0.87-1.00)	0.93‡ (0.86-0.996)	0.91‖ (0.84-0.98)
Adjusted† incident rate ratio	1.00	0.98 (0.90-1.07)	0.93 (0.86-1.01)	0.90‖ (0.83-0.98)

*Calculated from robust standard error due to under-dispersion in data

†Adjusted for age, sex, race, ethnicity, insurance type, emergency department visit, hospitalization, Charlson comorbidity index, LVEF, and AHRQ socioeconomic status index

‡$p<0.05$

‖$p=0.01$

ARNI – angiotensin receptor neprilysin inhibitor; PDC – proportion of days covered; IRR – incident rate ratio; CI – confidence interval; LVEF – left bentricular ejection fraction; AHRQ – agency for healthcare research and quality