Relationship of the Magnitude of Member Cost-Share and Medication Persistence With Newly Initiated Renin Angiotensin System Blockers

Dongmu Zhang, PhD; Angeline M. Carlson, PhD; Patrick P. Gleason, PharmD;
Stephen W. Schondelmeyer, PhD; Jon C. Schommer, PhD; Bryan E. Dowd, PhD;
and Alan H. Heaton, PharmD

ABSTRACT

BACKGROUND: Effective treatment for chronic diseases often requires medication refill persistence. Health plans have frequently increased the amount of member cost-sharing by implementing tier-copayment pharmacy benefit designs and raising copayments. However, increased member cost-share may present a barrier to the management of chronic conditions. Little is known about the relationship between the magnitude of member cost-sharing and antihypertensive persistence among members newly initiating therapy.

OBJECTIVE: To investigate and quantify the relationship between amount of prescription cost-sharing and medication refill persistence among members newly initiating therapy with a single-agent angiotensin system blocker— either an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB).

METHODS: This was an observational cohort study of pharmacy and medical claims data for 29 employers with approximately 310,000 beneficiaries that did not have a change in pharmacy benefits including the amount of member cost-share in 2004. The claims data were supplemented with census data for household income and race at the Zip Code level. Selected patients were new users of single-agent ACEIs or ARBs (i.e., excluding ACEI or ARB in combination with hydrochlorothiazide or amlopdipine) between January 1 and June 30, 2004, without a pharmacy claim for an ACEI or an ARB in the 6 months prior to the index claim for either drug type. Medication refill persistence was measured in 3 ways: (1) total number of days without ACEIs or ARBs during 6 months follow-up, (2) proportion of days covered (PDC) with less than 80% defined as nonpersistent during 6 months follow-up, and (3) number of days to the first gap of more than 30 days in medication coverage from the index date to end of 2004 (mean [SD] follow-up = 9.2 [1.8] months). Three statistical models were fit: Tobit model, examining the association between cost-sharing and total number of medication gap days; logistic regression, testing the association between cost-sharing and odds of being nonpersistent; and Cox proportional hazards model, assessing the association between cost-sharing and time to a 30-day gap.

RESULTS: Among the eligible population, a study cohort of 1,351 members newly initiating a single-agent ACEI or ARB was identified. These members were 41.8% female and had a mean age of 55.9 (SD = 13.1) years. On average, their member cost-share was $12.42 (SD = $8.50) per 30-day supply. Each $1 increment in per 30-day cost-share was associated with a 1.9% increase in total gap (β = 0.019, 95% confidence interval [CI], 0.007-0.030, P = 0.001), a 2.8% increase in the odds of being nonpersistent (odds ratio [OR] = 1.028, 95% CI, 1.011-1.045, P = 0.001), and a 1.0% increase in the risk of having a gap of more than 30 days (hazard ratio [HR] = 1.010, 95% CI, 1.001-1.019, P = 0.034). Following transformation of the cost-sharing coefficient in each model, a $10 increment in cost-share had a consistent negative influence; 18.9% greater total gap days (β = 0.189, 95% CI, 0.073-0.304), 31.9% greater odds of being nonpersistent (OR = 1.319, 95% CI, 1.120-1.553), and 10.2% larger hazard of having a gap of more than 30 days (HR = 1.102, 95% CI, 1.007-1.205).

CONCLUSION: For members newly initiating single-agent angiotensin system blocking medication, the amount of prescription cost-sharing was associated with a negative impact on refill persistence.

What is already known about this subject

- In a quasi-experimental (pre-post with comparison group) study, rates of persistency with antihypertensive therapy were not significantly affected by the implementation of a cost-share increase of $13 per prescription for 29% of antihypertensive use and $1 to $3 for the remaining 71% of antihypertensive use.

- When comparing antihypertensive persistence among 3 benefit tiers (generics, preferred brands, and nonpreferred brands), using the measure of proportion of days covered, researchers have found an inverse association between cost-share and persistence.

- The quantitative relationship between antihypertensive cost-sharing and persistence among members newly initiating therapy is unknown.

What this study adds

- Among members newly initiating angiotensin system blocking medication, each $1 increment in member cost-share for the initial prescription claim was associated with 2.8% greater odds of being nonpersistent at 6 months after initiating therapy.

- Among members newly initiating angiotensin system blocking medication, each $1 in member cost-share for the initial prescription claim was associated with a 1.9% increase in total medication gap in therapy.

- The magnitude of member cost-share was found to have a consistent effect on medication persistence by 3 measures: total gap, odds of being nonpersistent, and risk for a 30 day gap.

Outpatient prescription drug spending in the United States was $200.7 billion in 2005 with a 5.8% increase over 2004.[1] To control rising prescription drug costs, managed care organizations (MCOs) and the employers with whom they contract began utilizing multitiered formularies after the early 1990s.[2] To offset the continued increase in prescription drug spending, many health plans have increased prescription cost-sharing across all copayment tiers.[2] In 2006, the most common commercial pharmacy benefit design employed 3-tier copayments with average member cost-share of $11 for

generic drugs, $24 for preferred brand-name drugs, and $38 for nonpreferred brand-name drugs.[3]

One rationale behind prescription cost-sharing is to make consumers sensitive to prescription costs so that they will limit "nonessential" use and utilize generic or less expensive branded drugs when needed. In a recent literature summary of 65 studies, researchers examined prescription drug cost-sharing associations with medication and medical utilization and spending.[4] Using an unspecified meta-analytic calculation methodology, the authors found that for each 10% increase in cost-sharing, prescription drug spending decreased by 2% to 6%, dependent upon the drug class and the patient conditions. In a statistical model derived from a cross-sectional analysis of claims data from 25 employers, it was estimated that doubling a member's copayment was associated with a 22% to 35% reduction in average annual prescription drug spending per member, with a proportional reduction in utilization.[5] Other well-designed studies assessing pharmaceutical utilization and spending associated with changes to the pharmacy benefit design, as defined by Goldman et al., demonstrated similar trends in decreased utilization and costs associated with increased cost-share.[6-23] However, in several of the better designed (e.g., pre-post with comparison group) studies evaluating the effect of benefit design changes, which result in higher cost-share to some members, researchers found much smaller decreases in utilization than observed in the cross-sectional studies. These authors also found significant shifts from nonpreferred products to preferred products, one of the desired outcomes of multitier pharmacy benefit designs.[14-15,20-22] A pre-post comparison of utilization of diabetes medication suggested that a greater than $10 increase in cost-share is necessary to induce a significant decrease in utilization.[11]

An unintended consequence of large increases in cost-sharing with subsequent large reductions in prescription drug spending may be that members forgo "essential" medication use, raising concern about adverse health outcomes, particularly for individuals with chronic illness.[9] In a well-designed pre-post with comparison group study, the authors found no significant differences in medical utilization, including inpatient hospital admissions, emergency room visits, and office visits, following implementation of a copayment increase.[21-22] That study also found that rates of persistency with antihypertensive and antilipidemic therapy were not significantly affected by the copayment change. The minimal association between medical outcomes and pharmacy cost-share in that study may in part be due to the small increases in cost-sharing most members experienced; cost-sharing went from a 2-tier structure of $7 and $12 to a 3-tier of $8, $15, and $25. Based on pre-implementation claims, only 14% of overall utilization, 29% of antihypertensive utilization, and 11% of antilipidemic utilization were subject to the largest increase in cost-share from $12 to $25. All other members' cost-sharing went from either $7 to $8 or from $12 to $15.

In addition, an assessment of a Canadian provincial health system change in prescription coverage from $2 copayment per prescription to 25% coinsurance with income-based out-of-pocket annual maximums showed no dramatic differences in persistence or in cardiovascular outcomes in a pre-post design.[24] This Canadian study is limited because it is not possible to quantify the individual difference in cost-share per prescription, and the U.S. health system lacks a comparable type of benefit design with income-based annual out-of-pocket maximum cost-share.

It is important to develop an understanding of the incremental effect that member cost-sharing has on "essential" medication persistence, especially for members newly initiating medication therapy. Among cardiovascular medications shown to reduce medical events, such as antihypertensives and lipid-lowering therapy, a handful of researchers have examined the association between prescription cost-sharing and medication persistence, but without consistent results.[6-9,14,17,20,23-27] These studies have consisted of a mix of users newly initiating and those currently on therapy. Another limitation of these studies is inconsistency in the definition of persistence and persistence measurement methodology.[28] Therefore, it is difficult to make comparisons between studies.

Persistence is generally measured in 3 ways, as a function of: (1) medication possession ratio (MPR) or proportion of days covered (PDC); (2) medication availability at a fixed time point; or (3) gaps in medication coverage.[29] Even though quasi-experimental study design (pre-post with comparison group) has good internal validity, it can only examine whether there is an impact of prescription cost-sharing on persistence based on the magnitude of cost-sharing change. The fixed cost-sharing in pre-post comparison studies does not allow assessment of a continuous quantitative relationship between cost-share and persistence. Furthermore, in pre-post comparison studies, not only the effects of prescription cost-sharing, but also the responses toward a pharmacy benefits change, are measured. In most cross-sectional studies, cost-sharing is either assessed by a price index or approximated by formulary tiers, neither of which measures members' actual economic burden. To our knowledge, at the time of this research, no one had investigated members newly initiated on therapy and the associated proportional effect of prescription cost-sharing on the level of nonpersistence. Finally, the main purpose of most of the published studies was to quantify the impact of a change in cost-sharing on prescription drug utilization, expenditure, and persistence.[8-9,14,17,20,24]

To our knowledge, the studies of cardiovascular drugs in which authors have attempted to quantify mathematically the relationship between cost-share and persistence were in the statin drug class [6,7,25] or focused on congestive heart failure patients.[23] Two antihypertensive studies evaluating the relationship between persistence and member cost-share focused on differences in persistence between 3 copayment tiers using the PDC metric.[26,27] Both of the antihypertensive studies found that

higher cost-share was a significant independent negative predictor of persistence. However, the studies are limited due to the use of 1 persistence measure and the inability to quantify the relationship between the amount of cost-share and persistence.

The objective in this study was to investigate and quantify the influence of the amount of prescription cost-share on medication refill persistence among members newly initiating angiotensin system-blockers: angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). ACEIs and ARBs are primarily prescribed for hypertension[30] and have been associated with higher persistence rates than other antihypertensive therapeutic classes.[31-33] They have a similar mechanism of action, reducing the effect of angiotensin II on the body, and nearly identical side effect profiles with a higher proportion of patients reporting cough with ACEIs.[34-35] The equivalent effectiveness and safety of ACEIs and ARBs has been recently reported in the Agency for Health Research and Quality document "Comparative effectiveness of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARBs) for treating hypertension."[35]

During the present study, 6 single-agent ACEIs were available by generic name (captopril, enalapril, fosinopril, lisinopril, moexipril, and benazepril), 4 single-agent ACEIs were available as brand only (trandolapril, perindopril, quinapril, and ramipril), and all single-agent ARBs were available as brand only. This distribution of study drugs across copayment tiers permits analysis of the relationship between cost-share amount and persistence.

■ METHODS

This observational cohort study used a Midwest commercial insurer's medical and pharmacy administrative claims data for health benefit services provided to 1.7 million members. To be eligible for analysis, members were required to have been continuously enrolled from July 1, 2003 to December 31, 2004 with a health plan group, pharmacy benefit, and cost-share that did not change during 2004. There were 29 employers that met these criteria, representing approximately 10% of the total membership of this commercial insurer. From these 29 employers, we identified new users of single angiotensin system-blocking (ACEI or ARB) agents. Combination products were excluded because the single angiotensin system-blocking agents are associated with significantly higher persistence rates than other antihypertensive drug classes.[36] By limiting the analysis to single-agent angiotensin system blockers, we reduce the potential for agents such as hydrochlorothiazide in combination products to negatively influence persistence. A new user was defined as an individual who started treatment with ACEI (Medi-Span's 6-digit Generic Product Identifier [GPI] code 361000) or ARB (code 361500) single agents (excluding ACEI/calcium channel blockers, ACEI/hydrochlorothiazide, and ARB/hydrochlorothiazide combinations) between January 1, 2004

and June 30, 2004 with no ACEI or ARB single agents or combinations dispensed in the 6 months (180 days) preceding the index date.

The first pharmacy claim for an ACEI or ARB single agent was defined as the index event, and the date of the index pharmacy claim was defined as the index date. The new users had to meet several inclusion criteria: (1) 18 years of age or older on the index date, (2) at least 28 days supply in the index pharmacy claim, (3) no facility hospitalization or long-term care claim of any duration after the index date, and (4) no diagnosis of dementia (ICD-9-CM codes 290.xx, 294.1x, 331.0x, 331.1x or 331.2x). Members were followed for 2 periods: from the index date to 6 months after the index date and from the index date to the end of 2004.

Variables

Medication refill persistence was measured 3 ways based on days supply recorded in pharmacy claims to quantify the intensity and duration:[28,29] (1) total gap or total number of days without medication during the first 6 months of treatment, (2) proportion of days covered (PDC) with less than 80% defined as nonpersistent (less than 144 days of coverage) during the first 6 months of treatment, and (3) time to a gap of more than 30 days in medication coverage from the index date to the end of 2004. Days supply that overlapped with previous pharmacy claims or extended past the observation period were not used in calculating persistence. Switching to a single-agent ARB or ACEI was counted as a continuation of treatment as long as the other criteria for continuation (e.g., no more than a 30-day gap) were met. However, members switching to a combination product or to an antihypertensive product in a different therapy class (e.g., beta blockers, calcium channel blockers) were defined as having terminated therapy on the date that the switch claim was filled. Members' out-of-pocket payment for the index prescription as recorded in pharmacy claims was used to measure cost-sharing after adjusting to a 30 days supply (cost-sharing for the initial claim was divided by days supply to yield cost-sharing per day, then multiplied by 30).

Control variables were selected according to Andersen's behavioral model of health services use[37] and previous empirical studies.[6-7,23,25,31-33,36,38-41] Andersen's model was originally developed in the late 1960s to explain how and why families use health services. This model has since been adapted to predict and explain prescription drug use.[42-44] According to the model, use of health services, including prescription drugs, is a function of patients' predisposing characteristics, enabling resources, and need factors. In this study, predisposing characteristics are those variables that describe the predisposition of individuals to continuously use an angiotensin system blocker; enabling resources describe the ability of patients to continuously obtain and use an angiotensin system blocker; and need factors describe the professionally determined requirements for continuous use of

an angiotensin system blocker.

Predisposing characteristics included age, gender, race, and whether a member previously used any antihypertensive medications other than ACEIs and ARBs. Because race is not available in claims data, it was controlled on an aggregate level using percentage of people who reported their race as white only in a member's Zip Code area based on the Census 2000 data.[45] Other antihypertensives included diuretics (General Product Indentifier Code beginning 37), beta-blockers (33), calcium channel blockers (34), antiadrenergic antihypertensives (3620), aldosterone receptor blockers (3625), direct vasodilators (364000), and antihypertensive combinations (3699) without ACEIs and ARBs.

Enabling resources included residence (urban, rural, or super rural); income; number of unique medications in prior 6 months; number of doctor visits from July 1, 2003 to the end of 2004; initial therapeutic class (ACEIs or ARBs); utilization of mail-order service at any time during follow-up; presence of a yearly out-of-pocket maximum in member's pharmacy benefits; and whether a member used any antidepressant medications: mirtazapine (GPI code 580300), trazodone (58120080), monoamine oxidase inhibitors (581000), selective serotonin reuptake inhibitors (SSRIs, 581600), serotonin norepinephrine reuptake inhibitors (SNRIs, 581800), tricyclic agents (582000), and miscellaneous antidepressants (583000) in the prior 6 months. Tricyclic agents were not coded as antidepressant medications in those members with a diagnosis of diabetes as these drugs are often used for diabetic neuropathy.

Zip Codes were used to classify members as living in an urban, rural, or super rural area according to the Medicare ambulance fee schedule of the Center for Medicare and Medicaid Services (CMS).[46] A rural area is defined as an area outside a Metropolitan Statistical Area (MSA) or a New England County Metropolitan Area, or an area within an MSA identified as rural using the Goldsmith modification.[47] A super rural area is defined as a rural area determined by the Secretary of Housing and Urban Development to be in the lowest 25th percentile of all rural population arrayed by population density.[48] An area that is not classified as a rural or super rural area is considered an urban area. Income was also controlled on an aggregate level using household median income in a member's Zip Code area based on the Census 2000 Data.[45]

Need factors controlled for included conditions that angiotensin system blocking medications are generally used to treat or conditions associated with treatment. These conditions were based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis and procedure codes recorded in medical claims between July 1, 2003 and December 31, 2004. Diagnoses included essential hypertension (ICD-9-CM 401.xx), myocardial infarction (410.xx, 411.0x, 412.xx, 414.8x, 429.7x), congestive heart failure (398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91,

404.93, 425.4x, 428.xx), cerebrovascular diseases (362.34, 430.xx-438.xx, 784.3x, 997.02, 38.12 (P), 38.42(P), diabetes (250.xx), and dyslipidemia (272.xx).

Statistical Analysis

Statistical analyses were conducted using SAS 9.1 (SAS Institute Inc., Cary, NC). Results were considered statistically significant at $P < 0.05$ (2-tailed). Descriptive statistics, numbers, and percentages for categorical variables and means and standard deviations for continuous variables were calculated. These descriptive results were also stratified by cost-sharing tertiles. Cost-sharing tertiles were constructed according to the frequency distribution of cost-sharing, with each containing about one third of the study members. Comparisons of control variables across cost-sharing tertiles were conducted with chi-square tests for categorical variables and analyses of variance (ANOVA) for continuous variables. Three statistical models corresponding to the 3 measures of medication refill persistence were performed: Tobit model (proc lifereg), logistic regression (proc logistic) and Cox proportional hazards model (proc phreg). All of these models adjusted for the same set of control variables.

The Tobit model was used to model the association between cost-sharing and total gap over the first 6 months of treatment. This approach is appropriate for a dependent variable with a distribution that is spread out over a large range of positive values but with a large proportion of observations at the value zero. In this study, total gap has such a distribution. Although a linear model could capture the expected value of such a dependent variable, a linear model will likely lead to negative predictions for some subjects. In the Tobit model, a natural logarithmic transformation of total gap is used to address the skewness in the distribution of total gap. Because the natural logarithm of zero is not defined, every patient's total gap is added by one. Normal distribution after log transformation is a critical assumption under the Tobit model. This assumption was examined using histogram of residuals (i.e., predicted total gap minus actual total gap). In this study, the histogram of residuals shows that the normal distribution assumption under the Tobit model is met (data not shown).

Logistic regression, which is appropriate for describing the relationship between a categorical dependent variable and a set of predictors, was used to examine the association between cost-sharing and being nonpersistent (PDC < 80%) during the first 6 months of treatment. The overall fit of the logistic model was assessed using the Hosmer-Lemeshow test. This test divides subjects into deciles based on predicted probabilities, then computes a chi-square from observed and expected frequencies. When the test is not significant (P value ≥ 0.05), the null hypothesis that the model fits the data well cannot be rejected. The logistic regression model in this study has a Hosmer-Lemeshow goodness-of-fit test P value of 0.10 suggesting that the

model fits the data ($\chi^2[8] = 13.27$).

Cox proportional hazards model with the Breslow method for ties was used to test the association between cost-sharing and time to a gap of more than 30 days from the index date to the end of 2004. The Cox proportional hazards model assesses the effects of different covariates on logarithm of rate (log[rate]), without assuming a constant rate over time. A crucial assumption of the Cox proportional hazards model is proportional hazards (i.e., the hazard of having an event at any given time for an individual in one group is proportional to the hazard at that time for a similar individual in the other group.) This assumption was examined by plotting the log-cumulative hazard functions against the log(t). For this study, the plot of log-cumulative hazard functions against the log(t) suggests that the proportional hazards assumption was satisfied (data not shown). Survival curves stratified by cost-sharing tertiles were shown after adjusting for all the control variables in the Cox proportional hazards model.

Patient Privacy

A limited data set was received after direct individual identifiers were removed to meet the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Year of birth and Zip Codes are allowed in limited data sets. This study was approved by the University of Minnesota's Institutional Review Board.
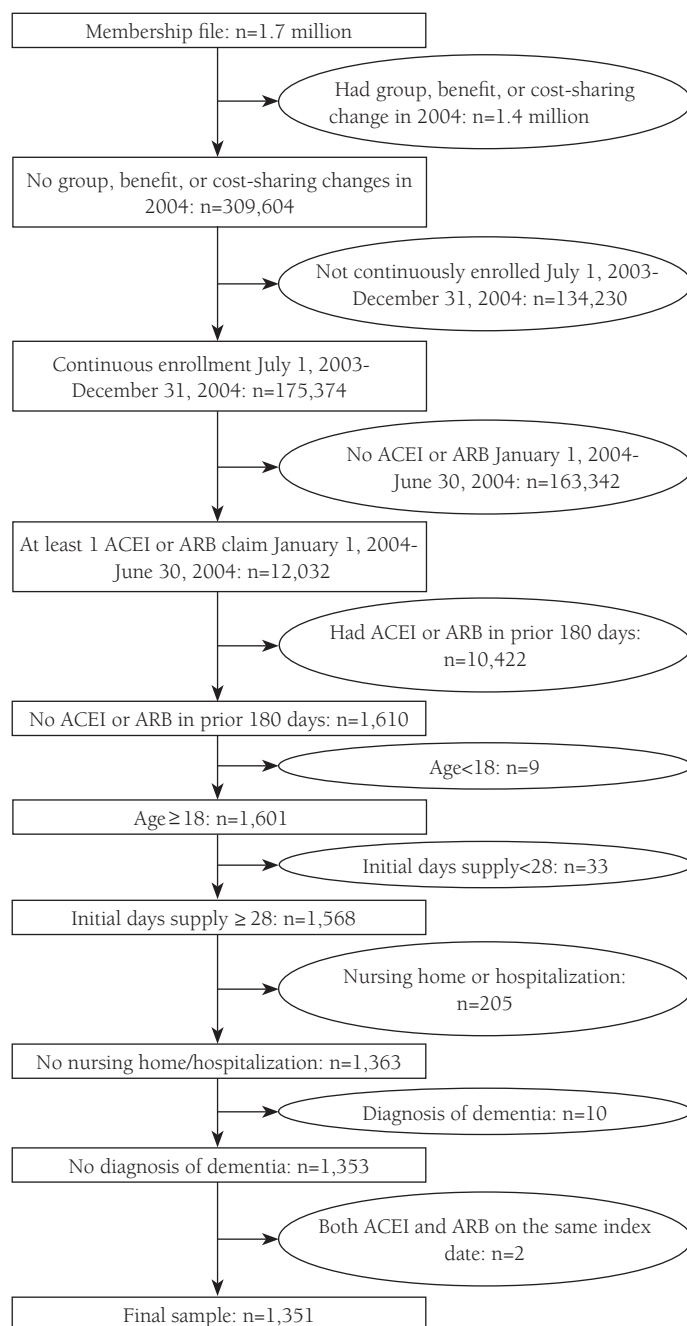
■ RESULTS

There were 175,374 members who were continuously enrolled from July 1, 2003 to December 31, 2004 with a health plan group, pharmacy benefit, and cost-share that did not change during 2004. A total of 1,610 new users of an angiotensin system-blocking single agent were found between January 1, 2004 and June 30, 2004. Two hundred and fifty-seven members were excluded due to the inclusion criteria (see Figure 1). Two additional members were excluded because they filled both an ACEI and an ARB single agent on the same index date. The final study cohort included 1,351 members.

Table 1 shows the members' pharmacy benefits designs. A majority of the members had a multitier formulary with 52.9% in a 2-tier copayment structure and 42.6% in a 3-tier structure. The use of a coinsurance-only pharmacy-benefits design was rare (0.4% of members) in this study cohort.

As shown in Table 2, the cohort was 41.8% female, with a mean age of 55.9 (SD=13.1) years (range=18-97). On average, study members initially paid $12.42 (SD=$8.50) for a 30 days supply of an angiotensin system-blocking agent. Extrapolations from the Zip Code census data indicate that the study members lived in relatively wealthy areas (mean of household median incomes for the Zip Code=$46,366 [SD=$14,449]) with the majority of residents being white (mean percentage of white people in the Zip Code=89.4% [SD=13.2%]). Characteristics of the study members were comparable across cost-sharing tertiles

FIGURE 1 Algorithm to Select the Sample of Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin II Receptor Blocker (ARB) New Users

TABLE 1 Pharmacy Benefits Design (N=1,351)

Benefits Design	Members (n)	%
Mandatory generic substitution*		
Yes	1,082	80.1
No	269	19.9
Formulary tiers†		
1 copayment tier	62	4.6
2 copayment tiers	714	52.9
3 copayment tiers	575	42.6
Type of cost-sharing‡		
Coinsurance only	6	0.4
Copayment only	1,011	74.8
Copayment and Coinsurance	334	24.7
Pharmacy deductible§		
Yes	113	8.4
No	1,238	91.6
Yearly out-of-pocket maximum‖		
Yes	613	45.4
No	738	54.6
Per-prescription out-of-pocket maximum¶		
Yes	62	4.6
No	1,289	95.4

** Mandatory generic substitution is defined as the member's benefit requires the
member receive a generic when a generic identical chemical entity is available.*

*† The most common copayment single-tier was $15 ($30 for 90 days for
mail order), 2-tier was $15/$30 ($30/$60 for mail order), and 3-tier was
$10/$20/$30 ($20/$40/$60 for mail order).*

‡ The most common coinsurance rate was 20%.

§ The most common pharmacy deductible was $100 per member per year   .

*‖ The most common yearly out-of-pocket maximum was $1,500 per member or
$2,500 per family .*

*¶ The most common out-of-pocket maximum per prescription was $40 ($120
for mail order)*

(Table 2). Members who paid the highest cost-sharing amount
for their initial claim were more likely to start with ARBs than
members who paid lower cost-sharing amounts. This is expected
because all ARBs were brand drugs and had higher cost-share
than ACEIs, which were mostly available as generics. In addi-
tion, members who were in the third cost-sharing tertile (highest
cost-sharing amount) lived in a Zip Code with lower household
median income, had fewer doctor visits, and were less likely to
have a yearly out-of-pocket maximum in their pharmacy
benefits design compared with the members in the other 2
tertiles. The second cost-sharing tertile had significantly fewer
members who used mail-order pharmacies and more members
who had a diagnosis of essential hypertension compared with

the first and third tertiles. These differences were adjusted in our
multivariate analyses.

During the first 6 months of treatment, the study members,
on average, had 53 (SD=52) days (range=0-152) without an
angiotensin system blocking agent. During the first 6 months,
8% of these members had no gap and 47% were classified as
being nonpersistent (PDC < 80%). From the index date to the
end of 2004, 54% of these members had a gap of more than 30
days with an average time to the gap of 172 (SD=108) days.

Results of the Tobit Model

Table 3 shows the results from the Tobit model. After controlling
for members' other characteristics, the coefficient of cost-
sharing was 0.019 (95% confidence interval [CI], 0.007-0.030,
$P=0.001$). Interpreting the coefficients in a Tobit model can be
challenging because the marginal impact of X on Y is nonlinear.
The approach is to take the Tobit estimate and multiply it by a
factor to obtain the marginal impact. The factor is the standard
normal cumulative distribution function at the sample mean
values of all the independent variables, which in our case was
0.98 (almost 1). Therefore, the Tobit model suggests that start-
ing at the mean values of all the independent variables including
cost-sharing, a $1 increase in cost-sharing was associated with
an approximate 1.9% increase in total gap. Following transfor-
mation of the cost-sharing coefficient, a $10 greater cost-share
was associated with an approximate 18.9% increase in total gap
(95% CI, 7.3%-30.4%).

Besides cost-sharing, 6 other significant independent
predictors were identified. A 1-year increase in age was associ-
ated with an approximate 1.2% decrease in total gap. Residing in
Zip Code areas with a higher prevalence of white residents,
using mail-order service, having an out-of-pocket annual
maximum on prescription drug spending, and having diagnoses
of dyslipidemia and myocardial infarction were also associated
with a lower total gap. Specifically, a 1% increase in the propor-
tion of white people in the member's Zip Code was associated
with a 1.1% decrease in total gap; members who used mail-
order service had a 86.4% lower total gap than those who did
not use mail-order service; members who had an out-of-pocket
annual maximum on prescription drug spending had a 29.7%
lower total gap than those who did not have this benefit; and
members who were diagnosed with dyslipidemia and myocar-
dial infarction had a 20.5% and 47.5% lower total gap compared
with those who did not have these diagnoses, respectively.

Results of Logistic Regression

Table 4 shows the results from the logistic regression model.
After adjusting for the control variables, a $1 increase in cost-
sharing was associated with a 2.8% increase in the odds of
being nonpersistent (odds ratio [OR]=1.028, 95% CI, 1.011-
1.045, $P=0.001$). Following transformation of the cost-sharing
coefficient, a $10 increase in cost-sharing was associated with a

TABLE 2 Characteristics of Study Members (N=1,351)

Variables	Copay Tertile 1	Copay Tertile 2	Copay Tertile 3	Total	P Value*
	$0.00-$8.30 n=452	$8.31-$13.00 n=455	$13.01-$127.98 n=444	$0.00-$127.98 n=1,351	
Mean initial cost-sharing per 30 days supply [SD]	6.29 [1.93]	9.45 [0.88]	21.71 [9.03]	12.42 [8.50]	<0.001
Predisposing characteristics					
Mean age in years [SD]	56.0 [12.7]	56.6 [12.8]	55.1 [13.7]	55.9 [13.1]	0.247
Female (%)	39.8	43.5	42.1	41.8	0.523
Other antihypertensives previously (%)	43.4	42.4	43.2	57.0	0.952
Mean % of white people in Zip Code [SD]	89.8 [13.2]	89.8 [12.4]	88.5 [13.9]	89.4 [13.2]	0.212
Enabling resources					
Residence (%)					0.584
Urban	64.8	60.7	61.5	62.3	
Rural	20.4	24.2	24.3	23.0	
Super Rural†	14.8	15.2	14.2	14.7	
Mean of the median income values for patients' Zip Codes [SD]	47,642 [14,480]	46,526 [14,015]	44,902 [14,751]	46,366 [14,449]	0.017
Mean number of unique medications in prior 6 months [SD]	3.9 [3.5]	3.7 [3.3]	4.2 [3.6]	3.9 [3.5]	0.088
Initiated with ACEIs (%)	96.9	92.5	44.6	78.2	<0.001
Mail-order service in 6 months follow-up (%)	16.2	12.3	18.2	15.5	0.045
Mean number of doctor visits July 1, 2003-December 31, 2004 [SD]	6.4 [7.8]	5.9 [7.5]	4.7 [7.3]	5.7 [7.6]	0.003
Depression (%)‡	15.7	15.0	15.5	15.4	0.946
Yearly out-of-pocket maximum (%)	53.8	47.9	34.2	45.4	<0.001
Need factors §					
Essential hypertension	73.2	83.3	74.3	77.0	<0.001
Myocardial infarction	7.3	4.4	5.9	5.9	0.176
Congestive heart failure	8.4	6.2	5.9	6.8	0.251
Diabetes	31.4	25.7	28.4	28.5	0.164
Dyslipidemia	50.7	49.9	53.4	51.3	0.548
Cerebrovascular disease	5.1	4.0	6.8	5.3	0.167
Days supply					
Mean total days supply in 6 months follow-up [SD]	164.7 [71.9]	143.0 [71.3]	142.4 [72.7]	150.1 [72.7]	<0.001
Mean total mail-order days supply in 6 months follow-up [SD]‖	186.7 [78.3]	164.8 [71.3]	168.1 [69.1]	173.7 [73.3]	0.166

*The statistical tests used to derive these P values were chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables.

† Super rural is defined as a rural area determined by the Secretary of Housing and Urban Development to be in the lowest 25th percentile of all rural populations arrayed by population density.[49]

‡ Depression was identified by looking at whether a member used any antidepressant medications: mirtazapine (GPI code 580300), trazodone (58120080), monoamine oxidase inhibitors (581000), selective serotonin reuptake inhibitors (SSRIs, 581600), serotonin-norepinephrine reuptake inhibitors (SNRIs, 581800), tricyclic agents (582000), and miscellaneous antidepressants (583000) in the prior 6 months.

§ Medical conditions in the "need factors" were identified using ICD-9-CM (the International Classification of Diseases-Ninth Revision-Clinical Modification) diagnosis and procedure codes recorded in medical claims between July 1, 2003 and December 31, 2004. Essential hypertension (ICD-9-CM 401.xx), myocardial infarction (410.xx, 411.0x, 412.xx, 414.8x, 429.7x), congestive heart failure (398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4x, 428.xx), cerebrovascular diseases (362.34, 430.xx-438.xx, 784.3x, 997.02, 38.12 (P), 38.42(P), diabetes (250.xx), and dyslipidemia (272.xx).

‖ Mean mail-order days supply in 6 months follow-up is derived from those members who used mail-order service during the 6 months follow-up.

ACEI=angiotensin converting enzyme inhibitor

TABLE 3	Results of the Tobit Model to Assess Association Between Cost-Sharing and Total Gap (N=1,351)			
Variables	Coefficient	95% CI		P Value
Initial cost-sharing per 30 days supply	0.019*	0.007	0.030	0.001
Predisposing characteristics				
Age	-0.012*	-0.019	-0.005	0.002
Female	0.111	-0.065	0.286	0.216
Pre-use of antihypertensives	0.100	-0.098	0.298	0.322
% of population self-reporting white race only	-0.011*	-0.018	-0.004	0.001
Enabling resources				
Living in rural area	0.153	-0.083	0.388	0.204
Living in super rural area†	0.076	-0.209	0.361	0.602
Household median income (thousands)	0.001	-0.007	0.008	0.888
Treatment for depression	0.093	-0.167	0.353	0.484
Initiated with ACEIs	-0.017	-0.253	0.220	0.891
Unique medications in prior 6 months (n)	-0.021	-0.054	0.012	0.206
Mail-order service	-0.864*	-1.121	-0.608	<0.001
Doctor visits July 1, 2003-December 31, 2004 (n)	0.000	-0.013	0.014	0.953
Yearly out of pocket maximum	-0.297*	-0.489	-0.105	0.003
Need factors				
Diagnosis of myocardial infarction	-0.475*	-0.853	-0.097	0.014
Diagnosis of congestive heart failure	0.088	-0.265	0.440	0.626
Diagnosis of cerebrovascular disease	0.397	0.005	0.789	0.050
Diagnosis of essential hypertension	0.002	-0.206	0.209	0.986
Diagnosis of diabetes	-0.077	-0.276	0.123	0.450
Diagnosis of dyslipidemia	-0.205*	-0.382	-0.029	0.023
Constant	4.884*	4.055	5.713	<0.001

Denotes statistically significant comparison, P<0.05.

LR x^2(20) = 147.35, P value<0.001, ACEI=angiotensin-converting enzyme inhibitor.
† Super rural is defined as a rural area determined by the Secretary of Housing and Urban Development to be in the lowest 25th percentile of all rural populations arrayed by population density.[49]

31.9% increase in the odds of being nonpersistent (OR=1.319, 95%CI, 1.120-1.553).

In addition to cost-sharing, 3 control variables were also significant in predicting the odds of being nonpersistent. A 1-year increase in age was associated with a 2.0% decrease in the odds of being nonpersistent. A 1% increase in the proportion of Caucasians in the member's Zip Code was associated with a 1.4% decrease in the odds of being nonpersistent. Members who used mail-order service had a 43.0% lower odds of being nonpersistent compared to those who did not use mail-order service.

Results of the Cox Proportional Hazards Model

Table 5 presents the results of the Cox proportional hazards model with the Breslow method for ties. Each $1 in cost share per 30-day supply was associated with a 1.0% greater risk of having a gap of more than 30 days in the coverage of ACEI or ARB single agents (hazard ratio [HR]=1.010, 95% CI, 1.001-1.019, P=0.034). Following transformation of the cost-sharing coefficient, a $10 increase in cost-share per 30-day supply was associated with a 10.2% increase in the risk of having a gap of more than 30 days (HR=1.102, 95% CI, 1.007-1.205).

Consistent with the Tobit model and logistic regression, age, residing in Zip Code census areas with a higher prevalence of white residents, and using mail-order service were also significant predictors of the risk of having a gap of more than 30 days in the coverage of ACEIs or ARBs. A 1-year increase in age was associated with a 1.1% decrease in the risk of having a gap of more than 30 days. A 1% increase in the proportion of white residents in the member's Zip Code was associated with a 0.8% decrease in the risk of having a 30 day gap. Members who used mail-order service had a 22.0% lower risk of having a gap of greater than 30 days than those who did not use mail-order service.

Figure 2 shows the estimated survival curves after adjusting for all control variables at the mean values in the Cox proportional hazards model. The survival curves were stratified by cost-sharing tertiles. The survivor function decreases over time and more dramatically in the higher cost-sharing tertile. After up to 1 year of follow-up, 10% more members in the lowest cost-sharing tertile ($0.00-$8.30) were still persistent (i.e., not having a 30 day gap yet) compared with those in the highest cost-sharing tertile ($13.01-$127.98).

■ DISCUSSION

Angiotensin system-blocking medication refill persistence intensity and duration among members newly initiating therapy were consistently found to be independently associated with cost-share. In addition, the relationship between medication persistence and cost-share, quantified as $1 greater cost-share, was associated with a 1.9% larger medication gap during the first 6 months of treatment. To our knowledge, these findings are the first to quantify the relationship between

TABLE 4 Results of the Logistic Regression to Assess Association Between Cost-Sharing and Odds of Being Nonpersistent (N=1,351)

Variables	Odds Ratio	95% CI		P Value
Initial cost-sharing per 30 days supply	1.028*	1.011	1.045	0.001
Predisposing characteristics				
Age	0.980*	0.970	0.989	<0.001
Female	1.125	0.892	1.418	0.320
Pre-use of antihypertensives	1.187	0.915	1.540	0.197
% of population self-reporting white race only	0.986*	0.976	0.995	0.003
Enabling resources				
Living in rural area	1.358	0.996	1.852	0.053
Living in super rural area†	1.172	0.806	1.703	0.407
Household median income (thousands)	1.001	0.991	1.010	0.906
Treatment for depression	0.871	0.618	1.227	0.429
Initiated with ACEIs	0.947	0.690	1.299	0.735
Unique medications in prior 6 months (n)	0.997	0.955	1.041	0.884
Mail-order service	0.570*	0.404	0.804	0.001
Doctor visits July 1, 2003-December 31, 2004 (n)	0.999	0.981	1.017	0.904
Yearly out of pocket maximum	0.907	0.704	1.168	0.449
Need factors				
Diagnosis of myocardial infarction	0.745	0.449	1.238	0.256
Diagnosis of congestive heart failure	0.993	0.619	1.593	0.975
Diagnosis of cerebrovascular disease	1.471	0.872	2.479	0.148
Diagnosis of essential hypertension	0.996	0.757	1.310	0.976
Diagnosis of diabetes	0.971	0.746	1.264	0.827
Diagnosis of dyslipidemia	0.843	0.668	1.064	0.150

* Denotes statistically significant comparison, P<0.05.
LR $x^2(20)$=97.82, P value<0.001, ACEI=angiotensin-converting enzyme inhibitor.
† Super rural is defined as a rural area determined by the Secretary of Housing and Urban Development to be in the lowest 25th percentile of all rural populations arrayed by population density.[49]

TABLE 5 Results of the Cox Proportional Hazards Model to Assess Association Between Cost-Sharing and Risk to Have a Gap of More Than 30 Days (N=1,351)

Variables	Hazard Ratio	95% CI		P Value
Initial cost-sharing per 30 days supply	1.010*	1.001	1.019	0.034
Predisposing characteristics				
Age	0.989*	0.983	0.996	0.001
Female	1.124	0.966	1.308	0.131
Pre-use of antihypertensives	1.130	0.951	1.342	0.165
% of population self-reporting white race only	0.992*	0.987	0.997	0.003
Enabling resources				
Living in rural area	1.150	0.942	1.404	0.169
Living in super rural area†	1.023	0.798	1.311	0.858
Household median income (thousands)	0.998	0.991	1.004	0.454
Treatment for depression	0.995	0.797	1.242	0.962
Initiated with ACEIs	0.925	0.759	1.129	0.445
Unique medications in prior 6 months (n)	0.998	0.971	1.027	0.901
Mail-order service	0.780*	0.627	0.969	0.025
Doctor visits July 1, 2003-December 31, 2004 (n)	1.003	0.991	1.015	0.641
Yearly out of pocket maximum	0.869	0.736	1.026	0.097
Need factors				
Diagnosis of myocardial infarction	0.908	0.648	1.272	0.575
Diagnosis of congestive heart failure	1.093	0.808	1.478	0.565
Diagnosis of cerebrovascular disease	1.265	0.916	1.747	0.153
Diagnosis of essential hypertension	0.972	0.812	1.164	0.761
Diagnosis of diabetes	0.921	0.774	1.097	0.359
Diagnosis of dyslipidemia	0.932	0.800	1.085	0.362

* Denotes statistically significant, P<0.05.
LR $x^2(20)$=62.40, P value<0.001, ACEI=angiotensin-converting enzyme inhibitor.
† Super rural is defined as a rural area determined by the Secretary of Housing and Urban Development to be in the lowest 25th percentile of all rural populations arrayed by population density.[49]

persistence and the amount of member cost-share for patients newly initiating angiotensin system-blocking medication.

Previously published studies focusing on pharmacy benefit design cost-sharing changes have shown minimal impact on antihypertensive persistence among current utilizers. These studies are not comparable to the present study because the subjects were current users and because the effect of a fixed benefit design change was being tested. In our cross-sectional study, members were newly initiating therapy and had variable per 30 day cost-share amounts ranging from $0 to $128

FIGURE 2 Survival Estimates by Cost-Sharing Tertiles from the Cox Proportional Hazards Model
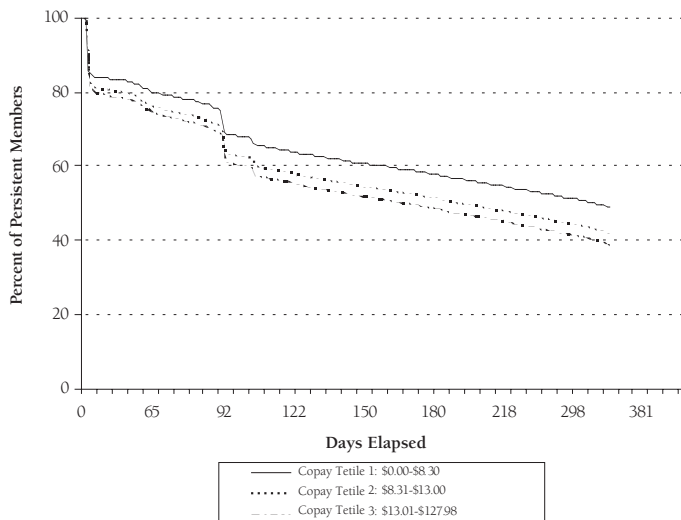
allowing us to quantify the associated relationship between cost share and persistence.

The results of this study are comparable to the findings of other persistence studies employing a cross-sectional study design. Among a combination of members currently utilizing and newly initiating statin therapy, Ellis et al. showed that higher member cost-sharing amounts were associated with large decreases in statin persistence rates.[25] As compared with members who had a copayment of less than $10, members who paid at least $10 but less than $20 and those who paid $20 or greater had 30% and 211% greater odds of being nonpersistent (cumulative multiple refill interval gap [CMG]>20%), respectively. A 30% greater odds of being nonpersistent when comparing a cost-sharing of $10 per 30 days supply to $20 is similar to the finding in this study of a 31.9% increase in the odds of being nonpersistent for a mean $12 versus $22 cost-sharing per 30 days supply. Taira et al. demonstrated that compliance with antihypertensive medications was significantly lower in higher than in lower copayment tiers.[27] As compared with members who used generics with a copayment of $5, members who used preferred brand-name drugs with a copayment of a $20 and those who used non-preferred brand-name drugs with a copayment of $20 to $165 had 24% and 52% less odds of being compliant, respectively. Thiebaud et al. found that higher cost-sharing was associated with lower statin utilization.[49] They reported that a $1 increase in brand drug and generic copay was associated with a 0.9% and 1.6% decrease in month-

ly days supply of brand drug and generics, respectively. These findings are similar to our finding that a $1 increase in cost-sharing was associated with a 1.9% increase in total gap.

We found that age, percentage of population self-reporting white only race in the patient's area of residence, and use of mail-order service were statistically significant predictors of total gap, being nonpersistent, and time to a gap of >30 days in the 3 models. Some empirical studies have shown that age and race were significant predictors of medication persistence.[31,36,38,40-41] Benner et al., for example, reported that members of black and other nonwhite races were less persistent with statin therapy.[41] Although we also found a significant association between persistence and race, this finding should be interpreted cautiously. Because claims data do not include race at the individual level, we measured race at an aggregate level (i.e., percentage of population in the patient's Zip Code area self-reporting white as their only racial group).

In addition, results of this study suggest that members who fill prescriptions by mail-order pharmacies have greater persistence rates. However, the impact of mail-order service may be artificial because the calculation of persistence in this study was based on days supply recorded in pharmacy claims. Mail-order pharmacies have larger days supply than community pharmacies. Within a fixed observation period, members who receive medications from mail-order pharmacies will have fewer refills than those who use community pharmacies and therefore the former group will be less likely to have a gap. We believe the impact of mail-order claims on our results is minimal because only 8.3% of all the claims and 18.0% of total days supply during the first 6 months of treatment are mail-order. In addition, mail-order was adjusted for in all 3 models. In order to remove the possibility of the impact of mail-order service on the outcome, the 3 models were rerun with restriction to members with community pharmacy claims only. The impact of cost-share on persistence did not change in all the 3 models (data not shown).

We also found that having an out-of-pocket annual maximum on prescription drug spending and having diagnoses of dyslipidemia and myocardial infarction were associated with a lower total gap in the Tobit model. We did not find similar relationships with the odds of being nonpersistent and the risk of having an unallowable gap in the logistic regression and Cox proportional hazards models. These differences in independent predictors between the Tobit model compared with the logistic regression and the Cox proportional hazards model may be due to the fact that the Tobit model allows for persistence (total gap) as a continuous variable, while the logistic regression requires persistence to be dichotomized (persistent vs. nonpersistent) and persistence is measured as time to an unallowable gap or duration in the Cox proportional hazards model.

We adapted Andersen's behavioral model of health services use as a conceptual framework to select important variables

to control in examining the relationship between cost-sharing and medication persistence. The results suggested that Andersen's model is valid as a guidance to select predictor variables for examining medication persistence. In this study, for example, the logistic model explained approximately 9% of the variance in medication refill persistence (pseudo-R^2=0.09). Our R^2 value is improved over that of Cole et al., who reported an R^2 value of 0.06.[23]

Limitations

The primary limitation of this study is its cross-sectional design, which is vulnerable to the effects of confounding factors. The 9% pseudo-R^2 value in our logistic regression model suggests that a substantial portion of the variance in medication refill persistence was not explained by our model, a problem typical of cross-sectional studies of this topic. Previous observational work has indicated that patients initiating treatments with generic drugs (lower cost-share) have somewhat higher adherence rates than do those initiating with brand drugs (higher cost-share); however, a randomized study is necessary for a rigorous test of the effects of initial cost-share on early medication persistence.[26] The need for further research is highlighted by recent quasi-experimental (pre-post with comparison) study of diabetic supply utilization before and after the implementation of a policy mandating provision of free diabetes supplies including glucose testing strips to patients with diabetes mellitus. Cross-sectional analysis documented an association between higher cost-sharing levels for the testing strips and lower compliance with blood glucose testing guidelines prior to implementation. Yet implementation of the free test strip policy was not associated with a change in adherence to testing guidelines, even among lower-income patients and those paying the highest cost-share prior to the policy change.[50]

Second, medication persistence is defined narrowly in the present study to include single-agent ACEI or ARB. While switching between single-agent ARB or ACEI was permitted, drug therapy was considered terminated if the patient switched to an ACEI or ARB in combination with hydrochlorothiazide (HCTZ) or to an antihypertensive in a different class such as a calcium channel blocker, diuretic, or a beta blocker. Third, our measurements of refill persistence depended on days supply recorded in pharmacy claims data. ACEI or ARB refill persistence may be underestimated in this study because other sources for acquiring prescription medications, such as free samples from physicians, could not be identified in claims data.

Fourth, the subjects of this study may have self-selected the Midwest commercial insurer as their health plan. Although pharmacy benefits are usually the same within one health plan and similar across different health plans for the same employer, this study may have been subject to a selection bias. However, to our knowledge, the pharmacy benefits were the same regardless of the health benefits selected by the member within one employer.

Fifth, the members of this study were mostly younger than 65 years. Therefore, the results of this study may not be generalizable to older adults.

Sixth, our results are limited to members newly initiating angiotensin system-blocking agents and may not be generalizable to established medication users or other drug classes. Seventh, we attributed interruption of refills to members' nonpersistence behavior. However, these interruption decisions may have been made by physicians as a result of ineffectiveness or side effects. Nonetheless, these decisions should affect members with lower and higher levels of cost-sharing equally. Eighth, some control variables, including income and race, were measured on an aggregate Zip Code level instead of on the individual level. Ninth, the duration of this study may be of concern to some readers. We followed the members for a minimum of 6 months and up to 1 year. The relatively short study duration was based on previous research, which has shown that the largest decrease in antihypertensive persistence occurs between 3 and 6 months after initiating therapy.[40,51]

Finally, in 2004, benazepril (Lotensin) and quinapril (Accupril) became generically available in February and December, respectively, resulting in lower member cost-sharing (i.e., generic cost-sharing). These 2 drugs were used by less than 5% of ACEI users and exclusion of these members in sensitivity analyses did not influence the results.

Policy Implication

This study has several implications for policy making. Payers have experimented with lowering medication cost-sharing for chronic diseases such as hypertension, hyperlipidemia, and diabetes, where medication has been shown to prevent morbidity and mortality.[52,53] Although zero-dollar member cost-sharing for selected chronic conditions has been proposed, a starting point may be a zero-dollar or near zero-dollar cost-sharing for generic drugs, which has been adopted by some employers.[54] A zero-dollar generic cost-share will potentially reduce cost to all beneficiaries and improve persistence; however, to our knowledge, currently there are no well-controlled studies indicating that zero-dollar cost-sharing improves medication adherence. Knowing a relationship exists between how much an individual pays for medication and how long he or she will remain persistent is the first step to improving pharmacy benefits designs. We echo the statements made by others: "The challenge remains to make individuals more sensitive to the cost of treatment without encouraging them to forgo cost effective care."[52]

■ CONCLUSION

This study adds to the literature through further quantifying the association between the amount of member prescription cost-share and medication refill persistence. Among members newly initiating an ACEI or ARB, a $10 greater cost-share was associated with 31.9% greater odds of being nonpersistent at

6 months after initiating therapy. To our knowledge, this is the first study to quantify the association between the dollar amount of member cost-share and total gap in therapy among members newly initiating ACEI or ARB therapy. For every $10 greater cost-share, we found an associated 18.9% increase in total medication gap during the first 6 months of follow-up. Further research is needed to validate these findings and to investigate this relationship among other antihypertensive drug classes and other chronic medications. Insurers should consider the impact that cost-share has on angiotensin system-blocking medication persistence when designing their pharmacy benefit offerings.

Authors

At the time the work was completed, DONGMU ZHANG was a PhD candidate, University of Minnesota, Minneapolis, MN. STEPHEN W. SCHONDELMEYER, PhD, and JON C. SCHOMMER, PhD, are professors of Social and Administrative Pharmacy, and BRYAN E. DOWD, PhD, is professor of Health Policy and Management, University of Minnesota, Minneapolis, MN; ANGELINE M. CARLSON, PhD, is president, Data Intelligence Consultants LLC, Eden Prairie, MN; PATRICK P. GLEASON, PharmD, is Director of Medical and Pharmacy Integration Services, Prime Therapeutics LLC, Eagan, MN; ALAN H. HEATON, PharmD, is Director of Pharmacy, BlueCross BlueShield of Minnesota, Eagan, MN.

CORRESPONDING AUTHOR:

Dongmu Zhang, PhD, Statistical Services, IMS Health, 960A Harvest Drive, Blue Bell, PA 19422. Tel.610-832-5808; Fax: 610-832-5850; E-mail: DZhang@us.imshealth.com

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