Associations of Renin-Angiotensin System Antagonist Medication Adherence and Economic Outcomes Among Commercially Insured US Adults: A Retrospective Cohort Study

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BACKGROUND: Medication non-adherence can result in considerable morbidity, mortality, and costs. The Pharmacy Quality Alliance hypertension medication adherence measure is used by US healthcare payers and providers to assess renin-angiotensin system antagonist medication adherence. However, associations between renin-angiotensin system antagonist adherence as calculated in quality measures, and healthcare service use and expenditure in commercial populations over a 1-year timeframe has not been assessed.

METHODS AND RESULTS: This retrospective cohort study used eligible commercially insured individuals from the Truven Health MarketScan Commercial Claims and Encounters Research Databases (2009–2015). Generalized linear models with log link and gamma distribution (expenditure) or negative binomial distribution (usage) assessed relationships between hypertension adherence (≥80% proportion of days covered) and healthcare use and expenditures (in 2015 US dollars) while adjusting for covariates (age, sex, geographic region; health plan; Deyo-Charlson Comorbidity Index, number of chronic medications, and treatment naivety). Beta coefficients were used to compute cost ratios and rate ratios. A total of 4,842,058 subjects were eligible; of those, 3,310,360 (68%) were adherent (adherent mean age 53.3±8.0 years, 55.9% men; non-adherent mean age 50.3±9.1 years, 53.1% men). Adherence was associated with fewer inpatient (rate ratios, 0.612; 95% CI, 0.607–0.617) and outpatient visits (rate ratios, 0.995; 95% CI, 0.994–0.997); and lower total costs (cost ratios, 0.876; 95% CI, 0.874–0.878) compared with non-adherence. Adherence was associated with lower average per member per month total costs ($97.98) compared with non-adherence.

CONCLUSIONS: Adherence to renin-angiotensin system antagonists was associated with fewer outpatient and inpatient visits, and lower total costs compared with non-adherence in a 1-year time frame.

Key Words: clinical outcomes ■ economic outcomes ■ hypertension ■ medication adherence ■ retrospective database analysis
Hypertension can be managed effectively with pharmacological agents such as renin-angiotensin system (RAS) antagonists that include 2 classes of drugs: angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.7,8 However, adherence to pharmacotherapy, defined as “the extent to which patients take medications as prescribed”,9 is needed to effectively manage the condition. While no standard adherence threshold exists, an individual is often considered “adherent” based on having proportion of days covered (PDC) or medication possession ratio of at least 80%.9

Individuals with chronic conditions such as hypertension are often non-adherent to their medications,10 although reported rates of adherence to anti-hypertensive medications vary depending on the definition used (eg, PDC, medication possession ratio), medication class, and population studied.11 A meta-analysis reported that adherent patients with hypertension had a 26% lower risk of a null or poor treatment and had almost 3 times the odds of a good outcome compared with their non-adherent counterparts.12

The Pharmacy Quality Alliance (PQA) is a multi-stakeholder, non-profit national quality organization that develops and stewards quality measures for medication use, including one that focuses on hypertension (RAS antagonists) adherence.13 Some PQA measures, including the RAS antagonist medication adherence measure, are used in the Centers for Medicare and Medicaid Services’ Star Rating System for Medicare Advantage Prescription Drug Plans and stand-alone Prescription Drug Plans,14 and as such are often used by health plans and medication therapy management providers to target their interventions.

However, the effect of adherence to RAS antagonists, as defined in the PQA quality measure specifications, has yet to be evaluated in a commercially insured population during a 1-year time frame. Furthermore, few studies have assessed the outcomes associated with adherence to RAS antagonists. This is important to investigate to justify the use of measures such as the PQA proportion of days covered: renin angiotensin system antagonists adherence measure in other populations (ie, commercially insured individuals), and to determine if the benefits of hypertensive medication adherence can be observed in the short-term (ie, 1 year). If they can, then this will serve as an incentive to patients and health plans to encourage medication adherence, with the goal of improved outcomes (eg, fewer healthcare service visits and lower healthcare costs). Therefore, the study aim was to describe the relationship between adherence status, as specified in the PQA PDC-renin angiotensin system antagonists adherence measure, and healthcare service use and expenditures over a 1-year period in a sample of commercially insured individuals. The study hypothesis was that adherent individuals would have lower healthcare service use and lower healthcare expenditures compared with non-adherent individuals.

**METHODS**

The methods and materials that support the findings of this study are available from the corresponding author upon reasonable request, however, the data would need to be obtained from the source.

**Data Source and Study Design**

This retrospective cohort study used a subset of Truven Health MarketScan Commercial Claims and Encounters Research Databases (2009–2015) to assess the relationship between adherence and healthcare service use and expenditures among individuals with commercial health insurance plans over a 1-year
period. The Truven Health MarketScan Research Databases provide de-identified healthcare records for >250 million patients\textsuperscript{15}; the de-identified data elements included: subject demographics; enrollment details; medical diagnoses and procedures; and prescription, inpatient, and outpatient administrative claims.

**Eligibility Criteria**
Study eligibility criteria were informed by the PQAs RAS antagonist medication adherence measure specifications.\textsuperscript{13} Individuals were eligible for inclusion if they: were aged ≥18 years at the index date (index date was defined as the first fill for a medication included in the RAS antagonist adherence measure after a 180-day baseline period that immediately preceded the 1-year study period); had continuous enrollment in their health insurance plan for 6 months prior and 12 months post-index date; and had at least 2 prescriptions dispensed for any medication included in the RAS antagonist adherence measure, with at least 150 days between the first and last prescription fill during the measurement period. Individuals were excluded if they had a diagnosis of end-stage renal disease based on the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) code of 585.6 during the measurement period in accordance with the PQAs measure specifications. Informed consent from participants was not required.

**Dependent Variables**
This study investigated the economic effects of associated adherence, namely associations with healthcare service use and expenditures. Healthcare usage consisted of the number of inpatient and outpatient visits during the 1-year measurement period. Healthcare expenditures consisted of all-cause inpatient, outpatient, prescription drug, and total expenditures during the 1-year measurement period. All expenditures were adjusted to 2015 US dollars using the consumer price index obtained from the US Department of Labor.\textsuperscript{16}

**Independent Variable and Covariates**
The key independent variable was adherence status, as defined in the RAS antagonist adherence measure using a threshold of 80% PDC.\textsuperscript{17} PDC is the proportion of days in the study period that the treatment regimen is available to the patient as observed from pharmacy claims data over the total number of days in the measurement period.

Potential confounding variables that served as covariates in statistical models included: age (in years at index date); sex; geographic region; health insurance plan type; Deyo-Charlson Comorbidity Index to capture comorbid conditions, with higher scores indicating greater comorbidity; the monthly average number of chronic medications (prescription days’ supply ≥28 to measure polypharmacy); and treatment naïve status (either existing or new users). Patients were considered “existing users” if they filled a prescription for a medication included in the RAS antagonist medication class during the baseline period, whereas “new users” included those who first filled a medication included in the measure on the index date (none during the baseline period).

**Statistical Analysis**
Generalized linear models with a log link and negative binomial distribution were used to describe the associations between adherence and healthcare service use (inpatient visits and outpatient visits). Generalized linear models with log link and gamma distribution assessed the relationship between adherence and healthcare expenditures (inpatient, outpatient, prescription drug, and total expenditure). Beta coefficients, generated from generalized linear models, were exponentiated ($e^\beta$) to compute cost ratios (CR) and rate ratios (RR) to demonstrate the difference in healthcare service use and expenditure between the adherent and non-adherent groups.\textsuperscript{18} Cost descriptions and CRs were used to calculate the average incremental adherence effect on per member per month (PMPM) costs.

Subject characteristics were assessed using t tests or Wilcoxon rank sum tests for continuous variables; and Chi square tests for categorical variables. All analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA). An alpha level of 0.001 was set a priori for all analyses. The University of Arizona Institutional Review Board approved this study.

**RESULTS**

**Study Sample**
Of the 16.2 million individuals with prescription claims data in the subset of Truven Health MarketScan Commercial Claims and Encounters Research Databases between 2009 and 2015, 4.9 million adults were eligible for inclusion in the RAS antagonist PDC calculation. After applying exclusion criteria, a total of 4,842,058 subjects were included in the 1-year study cohort. See Figure 1 for further details.

**Descriptive Analyses**
A total of 3,310,360 (68.4%) subjects were classified as adherent while 1,531,698 (31.6%) were classified as
non-adherent during the 1-year study period. There were significant differences between adherent and non-adherent subjects for all characteristics (all \(P<0.001\)).

Adherent subjects had a mean age of 53.3 years (SD, 8.0), were mostly men (55.9%), from the South region of the United States (43.4%), and were mainly insured by preferred provider organization health plans (63.0%). Low Deyo-Charlson comorbidity index scores were prevalent, with only 1.0% of the adherent group having a score of \(\geq 5\). The adherent group took a median of 2.5 (interquartile range, 3.0) chronic medications per month, and the majority (66.8%) were existing RAS antagonist medication users upon entering the measurement period.

Non-adherent subjects had a slightly lower average age of 50.3 years (SD, 9.1) and fewer men (53.1%) compared with adherent subjects; however, they had a greater proportion of individuals from the South region of the United States (50.6%). Similar to the adherent group, non-adherent patients were also predominantly insured by preferred provider organizations (62.6%), typically had low Deyo-Charlson comorbidity index scores (only 1.0% had a score of \(\geq 5\)). The non-adherent group took a median of 1.5 (interquartile range, 2.2) chronic medications per month, and were mostly (50.3%) existing RAS antagonist users. See Table 1 for detailed information about the characteristics of study subjects.

### Multivariable Analyses

In multivariable analyses that adjusted for potential confounding variables, adherence was associated with 38.8% fewer inpatient visits (RR, 0.612; 95% CI, 0.607–0.617) and a 0.5% fewer outpatient visits (RR, 0.995; 95% CI, 0.994–0.997) compared with non-adherence.

Adherence also was associated with lower inpatient (CR, 0.614; 95% CI, 0.613–0.615) and outpatient (CR, 0.912; 95% CI, 0.910–0.914) healthcare expenditure, yet higher prescription drug expenditure (CR, 1.216; 95% CI, 1.214–1.219). Total healthcare expenditure was 12.4% lower among adherent versus non-adherent subjects (CR, 0.876; 95% CI, 0.874–0.878). See Table 2 for detailed information about the adjusted multivariable analyses for healthcare use and expenditure.
The incremental PMPM cost of adherence status, compared with non-adherence, is depicted in Figure 2. Based on multivariable model results, on average, each adherent subject was associated with $93.84 lower inpatient, $34.51 lower outpatient, $33.30 higher prescription drug PMPM expenditures compared with non-adherent subjects. Adherence was associated with $97.98 lower total healthcare PMPM costs than non-adherence.

**DISCUSSION**

This study investigated differences, over a 1-year period, in healthcare service use and expenditure associated with RAS antagonist medication adherence, as defined in RAS antagonist adherence quality measure specifications, among a sample of commercially insured adults. This study has several key findings that address important gaps in the literature. Adherence to RAS antagonist medications had a large effect on the likelihood of using healthcare services and subsequent healthcare expenditures. Adherence associated effects were associated with lower total healthcare PMPM costs. The effects of RAS antagonist adherence were observed rapidly (ie, within 1 year). Additionally, this study is one of the first to evaluate the impact of RAS antagonist adherence on economic outcomes.

There is a dearth of published literature about the short-term effects (eg, within 1 year) of adherence on economic outcomes (eg, healthcare usage and expenditure) for patients with hypertension. Thus, the current study fills an important gap by providing evidence that adherence, as measured by proportion of days covered, to RAS antagonist medications was associated with improved economic outcomes, namely lower healthcare resource usage and overall expenditures. This trend is similar to Pitman et al who found that non-adherent individuals (medication possession ratio <80%) were more likely to have at least 1 hospitalization or emergency department visit and subsequently higher total healthcare costs.

Regarding healthcare service usage, adherence was associated with considerably fewer inpatient

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**Table 1. Characteristics of Adherent and Non-Adherent Study Subjects With Hypertension**

| Characteristic                      | Total (N=4,842,058) | Adherent (n=3,310,360) | Non-Adherent (n=1,531,698) |
|-------------------------------------|---------------------|------------------------|----------------------------|
| Region, n (%)                       |                     |                        |                            |
| Northeast                           | 604,265 (18.25)     | 222,811 (14.55)        |                            |
| North Central                       | 744,677 (22.50)     | 303,332 (19.80)        |                            |
| South                              | 1,436,308 (43.39)   | 775,703 (50.64)        |                            |
| West                               | 506,035 (15.29)     | 220,248 (14.38)        |                            |
| Unknown                             | 19,075 (0.58)       | 9604 (0.63)            |                            |
| Plan type, n (%)                   |                     |                        |                            |
| Comprehensive                       | 75,691 (2.29)       | 27,614 (1.80)          |                            |
| Exclusive provider organization     | 40,504 (1.22)       | 20,490 (1.34)          |                            |
| Health maintenance organization     | 440,590 (13.31)     | 214,937 (14.03)        |                            |
| Point of service                    | 235,797 (7.12)      | 111,189 (7.26)         |                            |
| Preferred provider organization     | 2,086,699 (63.04)   | 958,943 (62.61)        |                            |
| Point of service with capitation    | 19,183 (0.58)       | 9330 (0.61)            |                            |
| Consumer-directed health plan       | 138,441 (4.18)      | 71,292 (4.65)          |                            |
| High deductible health plan         | 75,881 (2.29)       | 35,807 (2.34)          |                            |
| Unknown                             | 197,574 (5.97)      | 82,096 (5.36)          |                            |
| Charlson Comorbidity Index, n (%)   |                     |                        |                            |
| 0                                  | 2,181,585 (65.90)   | 1,016,915 (66.39)      |                            |
| 1                                  | 776,458 (23.46)     | 363,037 (23.70)        |                            |
| 2                                  | 191,628 (5.79)      | 80,973 (5.29)          |                            |
| 3                                  | 105,931 (3.20)      | 46,124 (3.01)          |                            |
| 4                                  | 22,707 (0.69)       | 10,068 (0.66)          |                            |
| 5+                                 | 32,051 (0.97)       | 14,581 (0.95)          |                            |
| Average number of chronic medications in baseline, median (range) | 2.50 (3.00) | 1.50 (2.16) | |
| New user, n (%)                    | 1,098,512 (33.18)   | 761,841 (49.74)        |                            |

There were significant differences between adherent and non-adherent subjects for all characteristics in Table 1 (P<0.001).

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**Table 2. Adjusted Results From Generalized Linear Models for Healthcare Usage and Healthcare Expenditure of Subjects With Hypertension**

| Usage | Risk Ratio (95% CI) | Percent Difference |
|-------|---------------------|--------------------|
| Inpatient | 0.612 (0.607–0.617) | −38.8 |
| Outpatient | 0.995 (0.994–0.997) | −0.5 |

| Expenditure | Cost Ratio (95% CI) | Percent Difference |
|-------------|---------------------|--------------------|
| Inpatient | 0.614 (0.613–0.615) | −38.6 |
| Outpatient | 0.912 (0.910–0.914) | −8.8 |
| Prescription drug | 1.216 (1.214–1.219) | 21.6 |
| Total | 0.876 (0.874–0.878) | −12.4 |

*Healthcare usage was assessed using a generalized linear model with log link and negative binomial distribution adjusted for age, sex, plan type, region, Charlson comorbidity index, medication use status, average number of chronic medications used at baseline per month, and average number of renin-angiotensin system antagonist medications used during the study period per month.

†Percent difference reflects the difference in outcomes between the adherent group compared with the non-adherent group. It was calculated using the following formula: 1−e^β where β is the adherence beta coefficient from generalized linear models.

§Healthcare expenditure was assessed using a generalized linear model with log link and gamma distribution adjusted for age, sex, plan type, region, Charlson comorbidity index, medication use status, average number of chronic medications used at baseline per month, and average number of renin-angiotensin system antagonist medications used during the study period per month.

- Plan type: Comprehensive, Exclusive provider organization, Health maintenance organization, Point of service, Preferred provider organization, Point of service with capitation, Consumer-directed health plan, High deductible health plan, Unknown.
- Region: Northeast, North Central, South, West, Unknown.
- Plan type: Comprehensive, Exclusive provider organization, Health maintenance organization, Point of service, Preferred provider organization, Point of service with capitation, Consumer-directed health plan, High deductible health plan, Unknown.
- Region: Northeast, North Central, South, West, Unknown.
- Charlson Comorbidity Index: 0, 1, 2, 3, 4, 5+.
- Average number of chronic medications in baseline, median (range).
- New user, n (%): 1,098,512 (33.18).
visits, indicating fewer hospital admissions and emergency department visits. It is plausible that adherent patients may have been more likely to seek healthcare before their condition became severe enough to require inpatient care. While adherent individuals had fewer outpatient visits than the non-adherent group, the difference in usage was small (eg, 0.5%). A possible explanation is that adherent individuals manage their hypertension better by taking their medication and overall used fewer healthcare inpatient services, relying more heavily on outpatient services, while non-adherent individuals used more inpatient and outpatient services.

This study found lower healthcare expenditure, including overall, inpatient, and outpatient costs, were associated with RAS antagonist adherence. Others have identified similar results, for example, Kymes et al conducted a retrospective cohort study with commercially insured individuals taking antihypertensive medications using an medication possession ratio ≥0.80 to signify adherence. They found that individuals who transitioned from non-adherent to adherent status saved between $124 and $4423 in medical costs, depending on the number of comorbidities. Conversely, the authors also reported that those who transitioned from adherent to non-adherent status had increased annual expenditures ranging between $1706 to $7946.20

Others have attempted to estimate the costs associated with non-adherence in other settings. For example, Mennini et al used a prevalence-based probabilistic model to estimate that increasing the number of adherent patients (those taking at least 80% of the prescribed therapy) to 70% of the hypertensive population in 5 European countries could reduce cardiovascular-related healthcare costs by 332 million euros over a 10-year period.21

In this study, prescription drug expenditures were the only expenditure category that was higher among adherent patients. However, this is not surprising given that there is an expense associated with filling prescription medications that would not be incurred or incurred as frequently by non-adherent individuals. This current finding also correlates with Sokol et al who reported that greater adherence to chronic-disease medications (ie, for hypertension) was associated with higher medication costs, yet lower healthcare costs overall.22 Similarly, the current study found that overall expenditures were 12.4% lower for adherent patients, representing a saving of nearly $100 per person per month ($97.98), on average, for a total cost savings of roughly $1200 annually. These findings indicate the increased prescription drug costs associated with adherence are offset by reductions in medical expenditures.

Interestingly, the commonly held belief has been that the benefits (eg, better health, and lower healthcare use and costs) of taking chronic-disease medications (eg, RAS antagonists for hypertension) would not be observable for many years. However, the current study demonstrated that even within a 1-year timeframe, adherence was associated with lower healthcare expenditures compared with non-adherence. This is an important new finding that may help stimulate commercial health plans to encourage their members to remain or become adherent to their medication as the benefits can be realized over the short term and not limited to just the long term.

Finally, it is worth noting that roughly one third of the subjects were non-adherent (<80% PDC) to their hypertension medication. Thus, the current study provides supporting evidence that the prevalence of non-adherence to medications remains a significant

![Figure 2. Incremental cost of being adherent compared with non-adherent per member per month.](image)
opportunity in the United States, which concurs with the findings of previous studies.

Among a sample consisting of members from 13 managed care organizations, 75% of patients receiving monotherapy hypertensive medication were adherent based on an medication possession ratio of at least 80%. These adherent individuals were also associated with greater odds of having controlled blood pressure, compared with those with lower adherence. Another study using data from a medication event monitor (medication container with electronic time stamp) found ≈50% of patients prescribed an anti-hypertensive medication stopped taking them within a year that patients often omitted doses. Commercial health plans may consider utilizing the RAS antagonist medication adherence quality measure to monitor adherence levels within their populations to encourage innovation and opportunities to support a patient’s ability to be adherent. Poor adherence rates to anti-hypertensive medications is not limited to the United States. For example, Rami et al found that 53% (n=653) of hypertensive patients were adherent to their medication however; similar to the current study, they noted significant differences in adherence, based on demographic characteristics such as sex and race/ethnicity.

Finally, previous studies have offered strategies for improving adherence to anti-hypertensive medications including Petrilla et al who categorized them into: dosing and packaging modifications; patient counseling and education; clinical case management; reminder interventions as well as combinations of these strategies. Still, others have advocated for new studies and preventative strategies to address the considerable problem of untreated hypertension. To this end, Lee et al demonstrated that a pharmacy care program resulted in improved medication adherence and a clinically meaningful improvement in blood pressure. More recently, an interprofessional telehealth pilot program, involving physicians and pharmacists, demonstrated opportunities for improving medication quality among individuals with multiple chronic conditions, such as hypertension. These strategies, and other evidence-based interventions, should be leveraged to support a patient’s ability to be adherent. Future research could investigate the association of adherence on additional outcomes or clinical indicators for hypertension, such as change in blood pressure.

This study had several limitations. First and most notably, the current retrospective database study design has several important limitations. However, the current analyses did adhere to recommendations for analyzing hypertension adherence using retrospective data proposed by Halpern et al. The data used were originally intended for health insurance reimbursement purposes, and may contain billing and coding errors. Healthcare expenditures may have been overestimated given that they were: all encompassing (ie, captured expenses not directly related to hypertension), although this did allow a more holistic assessment of the association of medication adherence and healthcare expenditures; and may have included expenses that were later reversed outside the study period. Additional costs, such as insurance co-payments, were not included in the analysis and may have influenced subjects’ adherence to their medications. Additionally, adherence to other drug classes was not assessed. Adherence was calculated indirectly using prescription claims data, thus it was impossible to confirm whether the patients actually took the medication. Selection bias, whereby individuals in the adherent group were different from those in the non-adherent group, may also be present. While multivariable analyses accounted for differences between groups, the data were limited only to those individuals with administrative claims however, potential confounding may have remained because of unobserved demographic and clinical characteristics. For example, other potential confounding characteristics, such as race/ethnicity, education, access to healthcare, and socioeconomic status among others, may have an influence on the results but could not be accounted for because of data limitations. The available covariates used in the adjusted models were measured during the baseline period, thus may not be representative over time. Furthermore, while statistically significant, the differences between groups were small, thus the effects could potentially be attributed to the large sample sizes. Although treatment naïve status was captured to account for immortal time bias, individuals classified as current or new users may not fully minimize this bias. Finally, the Truven MarketScan Research Database is a convenience sample of commercially insured individuals which limits the generalizability of these study results to other populations.

CONCLUSIONS
Adherent individuals with a PDC ≥80%, in this sample of commercially insured adults taking RAS antagonists, were associated with lower healthcare usage and total healthcare expenditure over the 1-year study period. This important new finding demonstrates the economic benefits of promoting adherence among patients with hypertension to observe the short-term benefits of taking RAS antagonists.
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