

Antihypertensive Medication Adherence and Subsequent Healthcare Utilization and Costs

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Objectives: To evaluate the relationship between adherence to antihypertensive medications (AHMs) and subsequent hospitalizations, emergency department (ED) visits, and costs of care.

Study Design: Retrospective analysis of a national pharmacy benefits database of deidentified pharmacy and medical claims among patients with a diagnosis of hypertension. Adherence was estimated using the medication possession ratio (MPR).

Methods: Multivariate logistic and 2-part general linear models were estimated to study the relationship between adherence level (estimated by the MPR) and subsequent association with healthcare costs and cardiovascular (CV)-related hospitalizations and ED visits.

Results: We identified 625,620 patients with at least 2 claims for AHMs and divided them into 3 cohorts based on year 1 MPR of less than 60% (62,388 patients with low adherence), 60% to 79% (96,226 patients with moderate adherence), and 80% or higher (467,006 patients with high adherence). Patients with high adherence to AHMs were more likely to be older and male, have higher chronic disease scores and lower AHM copayments, and fill a greater percentage of prescriptions by mail order. Year 2 total mean (SD) adjusted healthcare costs were significantly lower for patients with an MPR of 80% or higher (\$7182 [\$27]) vs 60% to 79% (\$7560 [\$59]) or less than 60% (\$7995 [\$73]) ($P < .001$ for both). In addition, patients with low or moderate adherence had higher age- and sex-adjusted odds of CV-related hospitalizations (odds ratio [OR], 1.33; 95% confidence interval [CI], 1.25-1.41) and ED visits (OR, 1.45; 95% CI, 1.33-1.58) ($P < .001$ for both).

Conclusion: Adherence to AHMs is associated with significantly lower total healthcare costs and with significantly lower odds of CV-related hospitalizations and ED visits

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More than 74.5 million Americans have hypertension, with an estimated cost of \$76.6 billion per year.¹ Previous clinical trials in hypertension have shown that reduction of blood pressure is associated with significant decreases in the incidence of stroke, ischemic heart disease, congestive heart failure, and renal failure across age, sex, race/ethnicity, type of antihypertensive used, and severity of hypertension.^{2,3} Despite this benefit, it is estimated that only 35% of patients with hypertension achieve optimal control.^{3,4}

In observational studies, nonadherence to antihypertensive medications (AHMs) is an important factor in the failure to achieve better blood pressure control⁵⁻⁷ and is associated with a higher risk of hospitalization and mortality among patients with diabetes mellitus.⁸ Bramley et al⁷ found that high adherence to AHMs, identified as a medication possession ratio (MPR) of 80% to 100%, was associated with better blood pressure control compared with low-to-medium levels of adherence. Two recent studies describe an association between better adherence to AHMs and decreased subsequent cardiovascular (CV) events⁹ and stroke¹⁰ among patients with newly diagnosed hypertension, but neither study evaluated costs of care. A 2009 review of the importance of medication adherence relative to CV outcomes stated that there is a clear need for more research to better understand the association between adherence and healthcare costs because surprisingly little is known among populations with CV disease.¹¹

Pivotal earlier studies¹²⁻¹⁴ demonstrated that better adherence to AHMs is associated with reduced costs of care. However, results from these studies may have been influenced by analysis of adherence and costs in the same year, and all relied on data from the 1990s. In addition, these prior studies evaluated the effect of adherence on costs among limited populations that included a large employer¹⁴ and Medicaid populations.^{12,13}

Given the limitations of prior work and the growing recognition about the importance of medication adherence,¹⁵ more robust studies are needed to evaluate current cost implications associated with adherence to AHMs. The present national retrospective cohort study of 625,620 insured patients with a diagnosis of hypertension evaluated the relationship between adherence to AHMs in 2007 and hospitalizations, emergency department (ED) visits, and costs of care in 2008.

METHODS

Data were extracted from the information warehouse of Medco Health Solutions, Inc. The information ware-

In this article
Take-Away Points / p569
www.ajmc.com
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house is a data repository that includes deidentified demographic and pharmacy claims history, including retail and mail-order use. The information warehouse has deidentified medical claims data on more than 10 million patients that can be matched to pharmacy claims.

The study included all patients aged 18 to 63 years with an *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*, diagnosis of hypertension (codes 401.x-405.x), and with 2 or more claims within 1 primary class of AHMs, at least 1 of which was between July 1, 2007, and December 31, 2007, and another within 12 months before the last claim in 2007. We excluded patients with claims for cancer (codes 140.x-172.x and 174.x-208.x) or human immunodeficiency virus (codes 042.x-044.x), as these diseases can be associated with overwhelming pharmacy and medical costs independent of adherence to AHMs. In addition, we excluded patients who were not continuously eligible for prescription drug coverage; who did not have medical or pharmacy data from July 1, 2006, through December 31, 2008; or who were 64 years or older as of January 1, 2007, because the information warehouse of Medco Health Solutions, Inc, does not reliably receive complete medical claims for patients covered by Medicare. For analysis purposes, we defined year 1 as January 1, 2007, through December 31, 2007, and year 2 as January 1, 2008, through December 31, 2008 (Figure 1). The selection criteria were used to create a deidentified data set that was further analyzed for this study.

Adherence to AHM class was estimated by calculating the MPR, or the ratio of total days of medication supplied to total days in a period. The MPR is the accepted standard for evaluation of adherence using retrospective data because it is easy to calculate and performs as well as other claims-based estimates.¹⁶ The MPR was calculated based on the total number of days between the dates of the last fill in year 1 and the first fill in the 365 days before the last fill. This MPR evaluation included a look back through July 1, 2006, to provide a full year of data on adherence. For patients receiving multiple AHMs, the MPR was calculated for each AHM separately, and the overall MPR was the mean of the individual MPR values.¹¹ The MPR was capped at 100%, as it is unlikely that patients use AHMs at greater than the prescribed frequency.¹⁶

For the primary evaluation, we used year 1 MPR to classify the patients into the following 3 categories: high adherence (MPR, $\geq 80\%$), moderate adherence (MPR, 60%-79%), and low adherence (MPR, $< 60\%$). As a secondary analysis of costs of care, we divided the MPR into 5 levels (0%-19%,

Take-Away Points

Adherence to antihypertensive medications (AHMs) is associated with lower total healthcare costs and with reduced odds of cardiovascular-related hospitalizations and emergency department visits.

- High adherence to AHMs (medication possession ratio [MPR], 80%-100%) reduces adjusted total healthcare costs up to \$813 per patient annually compared with low or moderate adherence to AHMs (MPR, $< 80\%$).
- The relationship between medication adherence and healthcare costs was continuous and inversely proportional such that healthcare costs increased significantly as the MPR decreased.
- Benefits of improved adherence and evidence of total cost savings provide incentive for patient-, provider-, and health system-level interventions to improve AHM adherence.

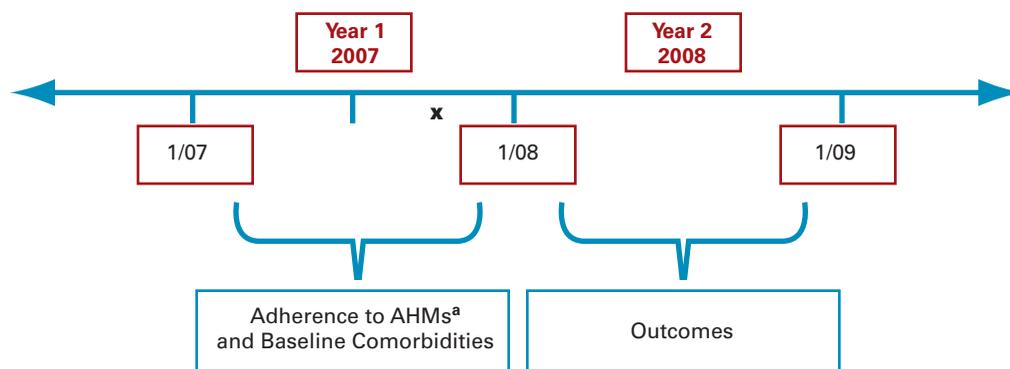
20%-39%, 40%-59%, 60%-79%, and 80%-100%). Previous literature recommends using the MPR as a dichotomous variable, with an 80% MPR considered adherent.^{15,16} Although this percentage is somewhat arbitrary, it has been accepted as the cutoff in most investigations on adherence and in observational and randomized controlled clinical trials.¹⁵

The number of total medications and different classes of AHMs on hand were determined as of December 31, 2007. In addition, we evaluated the following variables during year 1 that were identified as potential mediators of adherence: generic dispensing rates, the number of prescriptions filled for generically available AHMs divided by the total number of prescriptions for AHMs, the percentage of AHMs filled through mail order, the number of prescriptions filled by mail order divided by the total number of prescriptions filled after adjusting for the increased days supply by mail order, and the monthly patient copayment for AHMs from pharmacy claims, which is the total amount paid by the patient, including copayment, deductible, and coinsurance per month covered by prescriptions.

To control for possible comorbidities, we used pharmacy claims from 2007 to calculate a chronic disease score (CDS).¹⁶ The CDS is a comorbidity severity indicator derived from pharmacy-based claims data during a given period. For each patient, we used medical claims to evaluate the number of hospitalizations and ED visits in year 1 and year 2 and the following specific comorbidities identified by *ICD-9-CM* codes: coronary artery disease (codes 410.x-414.x and 996.03), dyslipidemia (code 272.x), stroke (codes 430.x-438.x and 997.02), heart failure (codes 402.x1, 404.x1, 404.x3, and 428.x), diabetes mellitus (code 250.x), end-stage renal disease (ESRD) (codes 403.x1, 404.x1, 585.5, and 585.6), and depression (codes 296.2x, 296.3x, 298.0, 300.4, 309.1, 309.28, and 311).

The primary outcome was total healthcare costs during year 2 (January 1, 2008, through December 31, 2008) for the groups having low-to-moderate adherence compared with the group having high adherence. In a secondary analysis, adjusted

■ **Figure 1.** Study Timeline for Data on Adherence to Antihypertensive Medications (AHMs), Baseline Comorbidities, and Outcomes



x Indicates that patients were required to have at least 1 AHM claim in the second half of year 1 and at least 1 other claim in the 365 days before the last claim in 2007.

^aAdherence to AHMs is based on the interval between the last claim in 2007 and the first claim in the prior 365 days and may extend into the last half of 2006.

total healthcare costs were also calculated for 5 quintiles of adherence. Total healthcare costs were determined by summing the costs of all pharmacy and medical claims (including outpatient services, hospitalizations, and ED visits) in 2008. Costs were based on total cost to the plan sponsor and excluded patient copayments and deductibles. Nursing home and home healthcare costs were not included in our cost analysis. Secondary outcomes were CV-related hospitalizations and ED visits, evaluated as the risk of having 1 or more medical claims indicating a hospitalization or an ED visit in 2008.

Statistical Analysis

We compared the baseline demographic factors, comorbidities, and medication factors between adherent and nonadherent patients using χ^2 test for binary variables and Wilcoxon signed rank test for continuous variables. Regression analyses were performed to assess the relationship between outcome variables and covariates. When the outcome variable had continuous values, we used general linear model (GLM) least squares regression analysis; when the outcome variable had binary values, we used logistic regression analysis. To reveal the determinants of adherence to AHMs, we created an outcome variable of high adherence versus low-to-moderate adherence. The predictors included demographics alone and together with comorbidities, CDS, class of AHMs, out-of-pocket cost for medication, and use of mail order. To explore possible differential effects of sex in critical subgroups of patients, we performed a secondary analysis of determinants of adherence that included interaction terms for sex-x-age, sex-x-coronary artery disease, sex-x-diabetes mellitus, sex-x-heart failure, sex-x-stroke, sex-x-hyperlipidemia, sex-x-depression, and sex-x-ESRD. We used logistic regression

analysis to evaluate the association of level of adherence with clinical outcomes of CV disease-related hospitalizations and ED visits after adjusting for important baseline differences. To determine the mean costs in year 2 for each level of adherence, we used GLMs and adjusted for baseline differences in age, sex, year 1 CDS, and year 1 total costs. Least squares means of costs were generated and compared among groups with the 3 levels of adherence. Version 9.1 of SAS (SAS Institute, Cary, NC) was used for all statistical analyses, and 2-sided $P < .05$ was considered statistically significant.

RESULTS

After applying the inclusion and exclusion criteria, we identified 625,620 patients for the analysis (Figure 2). On average, patients were 52.6 years old and 48.9% female and had an MPR of 86.3% and a CDS of 22.0 (Table 1). The most common comorbidities in the population included dyslipidemia (58.5%), diabetes mellitus (24.2%), coronary artery disease (11.0%), and depression (7.6%). At the end of year 1, patients averaged 3.7 medications on hand, representing 1.3 different classes of AHMs. Generic medications were used in 63.2% of AHMs, and 46.7% of patients received 1 or more of their AHMs by mail order. Angiotensin-converting enzyme inhibitors (43.9%) and diuretics (48.3% [84.5% of these were thiazides]) were the most common classes of AHMs used. The mean copayment for the AHMs was \$10.10 per month.

In year 1, using the prespecified categories of adherence, 467,006 patients (74.6%) demonstrated high adherence to AHM therapy (MPR, $\geq 80\%$), 96,226 patients (15.4%) demonstrated moderate adherence (MPR, 60%-79%), and 62,388 (10.0%) demonstrated low adherence (MPR, $< 60\%$). In Ta-

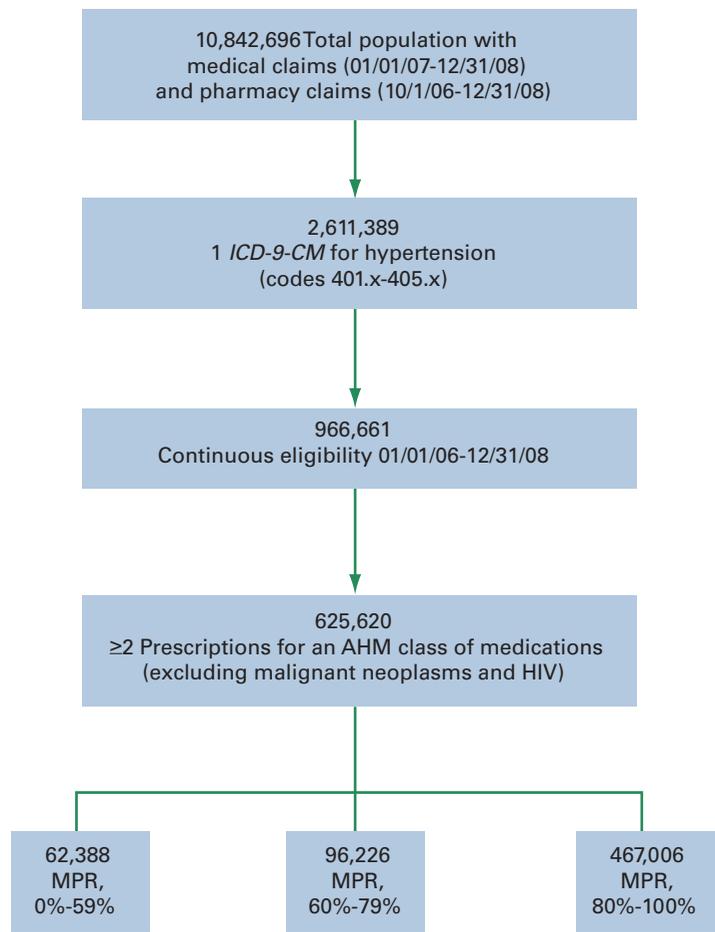
ble 2, we used logistic regression analysis to evaluate predictors of high adherence to AHMs versus low-to-moderate adherence. When adjusted for age, sex, and comorbidities, older patients were more likely to be adherent (odds ratio [OR], 1.03; 95% confidence interval [CI], 1.03-1.03), and female patients were less likely to be adherent (OR, 0.91; 95% CI, 0.90-0.93). In addition, dyslipidemia diagnosis (OR, 1.14; 95% CI, 1.13-1.15), higher CDS (OR, 1.26; 95% CI, 1.24-1.28), prescriptions for more than 1 class of AHMs at the end of year 1 (OR, 2.08; 95% CI, 2.02-2.13), and receipt of AHMs by mail order (OR, 2.24; 95% CI, 2.21-2.27) were associated with better adherence. The ORs for the sex-related interaction terms were not statistically significant.

In the multiple linear regression analysis evaluating the relationship between adherence in year 1 and costs of care in year 2 (**Table 3**), patients in the high adherence group had significantly lower total healthcare costs (\$7182) compared with patients in the moderate (\$7560) and low (\$7995) adherence groups ($P < .001$ for both). This represents lower total healthcare costs of \$387 to \$813 per patient for patients who are adherent to their AHMs ($P < .001$ for both). In a similar analysis, we adjusted for year 1 hospitalizations rather than year 1 total costs. The results of this additional analysis were similar to the results for the relationship between adherence and year 2 costs.

To determine if this association between adherence and costs was consistent across narrower ranges of adherence, we further subdivided adherence into 5 quintiles (0%-19%, 20%-39%, 40%-59%, 60%-79%, and 80%-100%) and determined adjusted costs for patients in each quintile. In **Figure 3**, adherence and adjusted total costs seem to have a linear relationship, with lower adherence associated with higher total costs. In addition, adjusted total costs at all levels of adherence were significantly higher compared with costs in the adherent group ($P < .001$ for all). Total costs of care for patients in the lowest adherence category (\$8427) were \$1246 higher than total costs of care for patients in the highest adherence category (\$7181).

During year 2, we identified 11,895 CV-related hospitalizations and 5150 CV-related ED visits in the study cohort. Hospitalization rates were 2.1%, 2.1%, and 1.8% among patients with low adherence, moderate adherence, and high adherence, respectively (**Table 4**). Emergency department visit rates were 1.0%, 0.9%, and 0.8% among patients with low adherence, moderate adherence, and high adherence, respectively. When adjusted for age and sex, patients with low adherence and

■ **Figure 2.** Flowchart of Patient Population



AHM indicates antihypertensive medication; HIV, human immunodeficiency virus; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; MPR, medication possession ratio.

moderate adherence were more likely to be hospitalized for a CV-related event (ORs, 1.33 and 1.28, respectively) and were more likely to have 1 or more CV-related ED visits (ORs, 1.45 and 1.27, respectively). When fully adjusted for baseline characteristics, the trend remained the same for risk of hospitalizations and ED visits; however, the differences only remained significant in the low-adherence group.

DISCUSSION

In this large retrospective analysis, patients diagnosed with having hypertension who were adherent to their AHMs in year 1 had \$387 to \$813 lower total healthcare costs and had decreased risk of CV-related hospitalizations and ED visits. These results suggest that patients who are nonadherent may not receive full benefit from their AHM therapy. In addition to worse clinical outcomes, nonadherence to AHMs results

■ **Table 1.** Characteristics of Patients by Adherence to Antihypertensive Medications (AHMs) in Year 1

Characteristic	Total (N = 625,620)	Medication Possession Ratio		
		0%-59% ^a (n = 62,388)	60%-79% ^a (n = 96,226)	80%-100% ^b (n = 467,006)
Age, mean (SD), y	52.6 (7.3)	50.1 (8.3)	51.4 (7.3)	53.2 (7.0)
Female sex, %	48.9	53.2	49.8	48.1
Medication possession ratio, mean (SD), %	86.3 (18)	44.2 (12)	71.7 (6)	94.9 (6)
Comorbidity, %				
Coronary artery disease	11.0	9.8	11.2 ^c	11.1
Diabetes mellitus	24.2	23.6 ^d	24.8	24.2
Dyslipidemia	58.5	50.1	55.2	60.4
Stroke	3.8	3.8	4.0	3.7
Congestive heart failure	2.3	2.8	2.8	2.1
Depression	7.6	8.8	8.5	7.3
End-stage renal disease	2.5	3.0	3.0	2.4
Chronic disease score, mean (SD)	22.0 (16.6)	18.9 (15.8)	21.1 (16.6)	22.6 (16.7)
Medications on hand the last day of year 1, mean (SD)				
Total medications	3.7 (3.1)	2.2 (2.4)	3.1 (2.8)	4.0 (3.1)
AHMs	1.3 (1)	0.7 (0.8)	1.1 (0.9)	1.5 (1.0)
AHM class, %				
β-Blockers	33.7	28.8	32.7	34.6
Calcium channel blockers	25.7	21.8	26.8	26.0
Angiotensin-converting enzyme inhibitors	43.9	38.4	42.5	44.9
Angiotensin receptor blockers	29.2	28.2	31.3	28.9
Diuretic	48.3	47.1	50.6	48.0
% Of AHMs generic, mean (SD)	63.2 (40)	62.8 (41) ^c	62.0 (40)	63.6 (40)
% Of AHMs received by mail order, mean (SD)	46.7 (47)	21.7 (38)	36.2 (45)	52.2 (7)
AHM copayment per month, mean (SD), \$	10.10 (10.70)	12.40 (22.20)	11.20 (9.30)	9.50 (8.40)
≥1 Hospitalizations, %	10.1	12.4	11.8	9.5
≥1 Emergency department visits, %	17.8	23.9	20.8	16.3
Total healthcare costs, mean (SD), \$	7474 (18,886)	7379 (22,169)	7970 (22,652)	7384 (17,506)

^aP values comparing groups with low and moderate adherence versus the adherent group using χ^2 test for categorical variables and Wilcoxon signed rank test for continuous variables. All P values significant at $P < .001$ unless otherwise indicated.

^bP value comparing trends across the 3 adherence groups using χ^2 test for categorical variables and linear regression analysis for continuous variables.

^cP > .05 compared with the adherent group.

^dP < .05 compared with the adherent group.

in higher total healthcare spending. Nonadherence was associated with greater healthcare utilization as demonstrated by CV-related hospitalizations and ED visits, which contribute to the increase in total healthcare costs seen in this population.

An earlier study¹⁴ from Medco Health Solutions, Inc, evaluated AHM adherence and costs in an insured population. Data were from a separate database than that used for this study and included patient claims from June 1997 to

May 1999. The study found a trend of lower total healthcare costs associated with higher adherence; however, the findings did not reach statistical significance among 7981 patients included in the hypertension cohort. In our analysis, increased drug therapy costs were offset by a corresponding decrease in medical costs in the adherent group, yielding clinically meaningful and statistically significant findings. The effect of adherence to AHMs on medical costs and risk of CV-related hospitalizations and ED visits is notable in

Antihypertensive Medication Adherence

Table 2. Multivariate Analysis of Predictors of Adherence in Patients Adherent to Antihypertensive Medications (AHMs) vs All Other Patients in Year 1

Variable	OR (95% CI) for Adherent Patients Versus All Other Patients	
	Age and Sex Adjusted	Fully Adjusted ^a
Comorbidity		
Coronary artery disease	0.89 (0.87-0.91)	0.86 (0.84-0.88)
Diabetes mellitus	0.91 (0.90-0.92)	0.79 (0.78-0.80)
Dyslipidemia	1.21 (1.19-1.22)	1.14 (1.13-1.15)
Stroke	0.84 (0.82-0.87)	0.93 (0.90-0.96)
Congestive heart failure	0.68 (0.65-0.70)	0.79 (0.76-0.82)
Depression	0.89 (0.88-0.91)	0.89 (0.87-0.91)
End-stage renal disease	0.75 (0.73-0.78)	0.79 (0.76-0.82)
Chronic disease score ≥22.0	1.24 (1.22-1.25)	1.26 (1.24-1.28)
Taking >2 AHMs	2.04 (2.00-2.09)	2.08 (2.02-2.13)
>80% Of AHMs received by mail order	2.44 (2.41-2.47)	2.24 (2.21-2.27)
AHM copayment per month >\$10	0.68 (0.67-0.70)	0.79 (0.78-0.80)
Hospitalizations in year 1	0.74 (0.73-0.75)	0.87 (0.85-0.89)
Emergency department visits in year 1	0.71 (0.70-0.72)	0.79 (0.77-0.80)

CI indicates confidence interval; OR, odds ratio.
^aAdjusted for age, sex, coronary artery disease, diabetes mellitus, dyslipidemia, stroke, congestive heart failure, depression, end-stage renal disease, chronic disease score, number of AHMs, percentage of AHMs received by mail order, AHM copayment, hospitalizations in year 1, and emergency department visits in year 1.

Table 3. Costs of Care per Patient With Hypertension^a

Medication Possession Ratio	Medications	Outpatient Care	Hospitalizations	Emergency Department Visits	Total Healthcare ^b
Unadjusted Costs of Care in Year 2, Mean (SD), \$					
0%-59% (n = 62,388)	1509 (3400) ^a	3776 (12,363) ^a	1913 (13,979) ^a	172 (879) ^a	7370 (22,206) ^a
60%-79% (n = 96,226)	1932 (3789) ^a	3705 (13,371) ^a	1759 (13,663) ^a	134 (679) ^a	7530 (22,601) ^a
80%-100% (n = 467,006)	2383 (3817)	3390 (11,147)	1386 (11,256)	101 (547)	7261 (18,709)
Adjusted Costs of Care in Year 2 for Age, Sex, Year 1 Chronic Disease Score, and Year 1 Total Healthcare Costs					
0%-59% (n = 62,388)	1880 (12) ^a	3887 (44) ^c	2057 (48) ^c	172 (2) ^c	7995 (73) ^c
60%-79% (n = 96,226)	2034 (10) ^c	3635 (35) ^c	1759 (38) ^c	131 (2) ^c	7560 (59) ^c
80%-100% (n = 467,006)	2317 (5)	3396 (16)	1366 (17)	102 (1)	7182 (27)

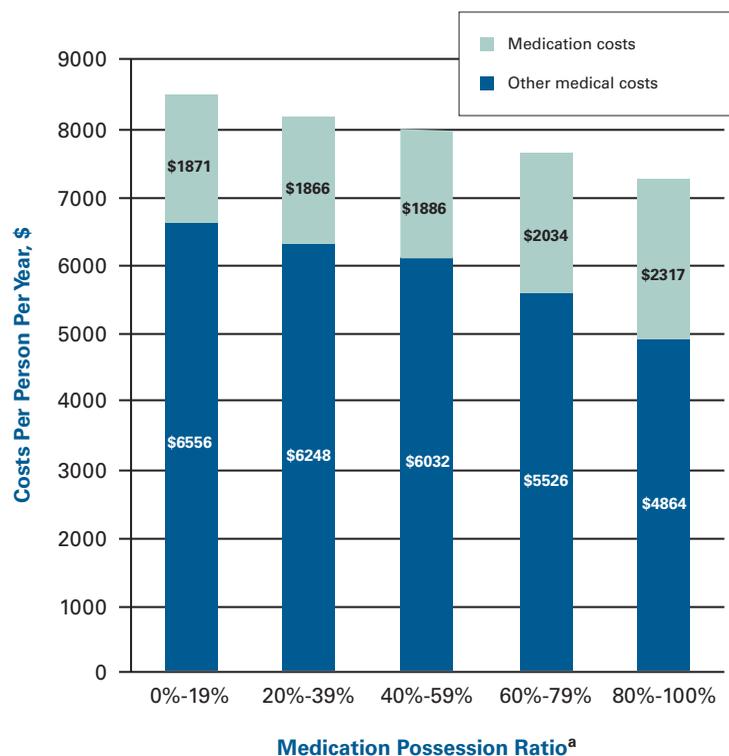
^aCosts are significant compared with the adherent group (medication possession ratio, 80%-100%) ($P < .001$).
^bTotal healthcare costs may vary due to rounding of individual component costs.
^cCosts are significant compared with the adherent group (medication possession ratio, 80%-100%) ($P < .001$).

this population of patients younger than 65 years. Based on age alone, this population is at lower risk for CV morbidity and mortality than adults 65 years and older.¹ It has been suggested that the primary benefits of hypertension treatment in young and middle-aged populations are due to reduction of subclinical organ damage rather than reduction in clinical events.¹⁷ However, our data suggest that AHM adherence in a younger population is associated with a decrease in clinical events, providing further evidence for the importance of

enhancing adherence to AHMs in patients of all ages with hypertension.

Based on the adjusted costs of care in Figure 3, the relationship between medication adherence and healthcare costs was continuous and inversely proportional such that healthcare costs increased significantly as the MPR decreased. The incremental medication costs in the group with low adherence were \$446, offset by a reduction in medical cost of \$1692, for a net savings of \$1246 per patient. Because these were ob-

■ **Figure 3.** Effect of Antihypertensive Medication Adherence on Adjusted Total Healthcare Costs by Level of Adherence (Medication Possession Ratio)



^aAll 4 lower quintiles were statistically significantly different compared with the medication possession ratio quintile of 80% to 100% ($P < .001$ for all).

servational data, we were unable to run a formal cost-benefit analysis. Based on the analysis shown in Figure 3, our results suggest that there may be an inverse linear relationship between AHM adherence and costs of care.

In our analysis, patients were more likely to be adherent if they were older and male, filled their prescriptions via mail order, and had dyslipidemia, higher CDS, more total medications, and prescriptions for more than 1 class of AHMs at the end of year 1. The finding that women had worse adherence is consistent with some^{9,18} but not all¹⁹ prior studies. Furthermore, results of the analysis of interactions between sex and age and between sex and each comorbidity suggest that in this study women were less likely to be adherent in younger and older age groups and among patients with and without each comorbidity. The association of higher CDS and more total medications with better adherence is consistent with findings from a recent study⁹ on AHM adherence in patients with newly diagnosed hypertension, which found that male sex, use of more than 5 concurrent medications, and diagnosis of dyslipidemia were predictors of better adherence. An explanation for this association is that symptomatic patients or patients

with poor understanding and perception of hypertension may be more motivated to adhere to their medication regimens because they perceive a greater risk of nonadherence.²⁰ However, the presence of most other CV comorbidities among our patients was associated with an increased risk of nonadherence in demographically adjusted and fully adjusted analyses. Further studies are needed to confirm and extend our understanding of the determinants of adherence in patients with hypertension, with particular attention to the role of comorbid conditions.

Cost of medications has previously been shown to be a risk for nonadherence.^{4,20} We found that lower (<\$10 per month) AHM copayments are associated with increased odds of adherence. The effect on cost may be mitigated by selection of different agents or by the use of retail versus mail order for the prescription. These findings confirm prior related research in which copayment level for AHMs, independent of other determinants, was found to be a strong predictor of adherence.²¹

Obtaining AHM prescriptions by mail order 80% or more of the time was also identified as an important independent predictor of better adherence. A likely explanation is that patients typically receive 90-day supplies via mail order and 30-day or more supplies via the retail channel. Obtaining a 90-day supply of medications may provide better odds of adherence because the patient has medication on hand for a longer period and has fewer opportunities to refill late. In addition, mail-order copayments for a 90-day supply are generally lower than retail pharmacy copayments for a 30-day supply. This effect needs to be evaluated in future studies to discern the influence of days supply versus pharmacy channel.

While several recent studies^{14,22-26} have demonstrated the association of AHMs with improved clinical outcomes in patients treated for hypertension, ours is the largest study to date that confirms this association between adherence and costs of care. The contributions of adherence to the total costs of care are complex because the influence of economic factors is difficult to estimate in clinical trials and in general medical practice,²⁷ which may be a reason why few studies evaluate the costs of care. Using data from 2007 to 2008, we were able to measure this association in a large insured population of insured patients.

This study has several limitations. First, we measured clinical outcomes using administrative claims data and did not have access to clinical information such as blood pressure

Table 4. Odds of Cardiovascular (CV)-Related Hospitalizations and Emergency Department (ED) Visits in Year 2^a

Medication Possession Ratio	CV-Related Hospitalizations			CV-Related ED Visits		
	Patients Having Hospitalizations, %	Sex- and Age-Adjusted OR (95% CI)	Fully Adjusted OR (95% CI)	Patients Having ED Visits, %	Age- and Sex-Adjusted OR (95% CI)	Fully Adjusted OR (95% CI)
0%-59% (n = 69,660)	2.1	1.33 (1.25-1.41) ^b	1.11 (1.03-1.20) ^c	1.0	1.45 (1.33-1.58) ^b	1.17 (1.06-1.29) ^b
60%-79% (n = 104,905)	2.1	1.28 (1.22-1.34) ^b	1.04 (0.99-1.10) ^d	0.9	1.27 (1.18-1.36) ^b	1.03 (0.95-1.12) ^d
80%-100% (n = 565,969)	1.8	1 [Reference]	1 [Reference]	0.8	1 [Reference]	1 [Reference]

CI indicates confidence interval; OR, odds ratio.

^aDetermined by general hospital claims for *International Classification of Diseases, Ninth Revision, Clinical Modification* codes for acute myocardial infarction (codes 410x-411x), previous myocardial infarction (code 412), angina pectoris (codes 413x), hemorrhagic stroke (codes 431-432), and ischemic stroke (codes 433-436).

^bP <.001 compared with the adherent group (medication possession ratio, 80%-100%).

^cP <.005 compared with the adherent group (medication possession ratio, 80%-100%).

^dNot significantly different from the adherent group (medication possession ratio, 80%-100%).

control, obesity, and smoking history, which affect CV risk. Furthermore, administrative claims may not capture medical care and costs that are not reported to the insurance company or are unrelated to home healthcare or nursing home care. The absence of these administrative claims could lead to the underestimation of costs.

Second, adherence was measured by pharmacy claims, and claims may not be recorded when patients receive medications from sources outside of the retail or mail-order claims process (eg, self-pay, sharing of medications, and use of samples). This lack of reporting could lead to an underestimation of adherence (MPR) for the patient. The advantage of the pharmacy claims database is that it fully captures retail and mail-order prescriptions for the patients. Despite this, the method we used for calculating the MPR is recommended for identification and evaluation of compliance and persistence with hypertension therapy using retrospective data, including diagnosis codes for hypertension and identification criteria.¹⁶

Third, it is possible that the association of adherence with lower costs and risks for hospitalizations and ED visits was due to an unmeasured confounder, as suggested by the “healthy adherer” effect²⁸ in which patients may adopt healthier lifestyles along with adherence behaviors. For example, some patients who were adherent to their AHMs may also be adherent to other CV medications such as statins, and the benefits associated with AHM adherence may be partially attributable to adherence to these other medications. In this study, adherent patients had a higher illness burden, as measured by CDS, and the association with outcomes persisted after adjusting for baseline variables (Table 2). In addition, Rasmussen and colleagues²⁸ found that patients who were adherent after myocardial infarction to statins and β-blockers had lower mortality than patients who were nonadherent, but adherence to calcium channel blockers was not associated with a mortality benefit. These findings provide further evidence that the ben-

efits of adherence to medications with proven efficacy may be more significant than a healthy adherer effect.

Fourth, because of the availability of accurate claims information, this study was conducted in patients aged 18 to 63 years. There is a possibility that the data may not reflect the adherence and costs of care for patients 65 years and older; however, based on the incidence of CV disease¹ and the understanding that adherence increases with age²⁹ and concomitant CV conditions,³⁰ adherence and costs should show similar results in older populations. Further studies of patients in this population are needed to confirm this assumption.

CONCLUSIONS

In this study, 25.4% of patients were nonadherent to AHMs, and these patients were more likely to have 1 or more hospitalizations or ED visits and had higher total healthcare costs. The medical benefits of improved adherence and the evidence of total cost savings provide clinical, quality, and economic incentives for patient-, provider-, and health system-level interventions to improve medication adherence in patients with hypertension. Further studies are required to confirm the effectiveness of such interventions that enhance adherence to medications and support clinician and provider interventions. This may be especially important as we move forward with quality and pay-for-performance initiatives.

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