Antihypertensive Medication Adherence, Ambulatory Visits, and Risk of Stroke and Death

James E. Bailey, MD, MPH^{1,2}, Jim Y. Wan, PhD², Jun Tang, MS³, Muhammad A. Ghani, MD⁴, and William C. Cushman, MD^{2,4,5}

¹Division of General Internal Medicine, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA;

²Department of Preventive Medicine, University of Tennessee Health Science Center, Memphis, TN, USA; ³Accredo Health Group, Inc., Memphis, TN, USA; ⁴Department of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA; ⁵Preventive Medicine Section, Veterans Affairs Medical Center, Memphis, TN, USA.

BACKGROUND: This study seeks to determine whether antihypertensive medication refill adherence, ambulatory visits, and type of antihypertensive medication exposures are associated with decreased stroke and death for community-dwelling hypertensive patients.

METHODS: This retrospective cohort study included all chronic medication-treated hypertensives enrolled in Tennessee's Medicaid program (TennCare) for 3–7 years during the period 1994–2000 (n=49,479). Health care utilization patterns were evaluated using administrative data linked to vital records during a 2-year run-in period and 1- to 5-year follow-up period. Antihypertensive medication refill adherence was calculated using pharmacy records.

RESULTS: Associations with stroke and death were assessed using Cox proportional hazards modeling. Stroke occurred in 619 patients (1.25%) and death in 2,051 (4.15%). Baseline antihypertensive medication refill adherence was associated with decreased multivariate hazards of stroke [hazard ratio (HR) 0.91; 95% confidence interval (CI), 0.86–0.97 for 15% increase in adherence]. Adherence in the follow-up period was associated with decreased hazards of stroke (HR 0.92; CI 0.87–0.96) and death (HR 0.93; CI 0.90–0.96). Baseline ambulatory visits were associated with decreased death (HR 0.99; CI 0.98–1.00). Four major classes of antihypertensive agents were associated with mortality reduction. Only thiazide-type diuretic use was associated with decreased stroke (HR 0.89; CI 0.85–0.93).

CONCLUSIONS: Ambulatory visits and antihypertensive medication exposures are associated with reduced

mortality. Increasing adherence by one pill per week for a once-a-day regimen reduces the hazard of stroke by 8–9% and death by 7%.

KEY WORDS: hypertension; ambulatory care; adherence; stroke; thiazide diuretics.

J Gen Intern Med 25(6):495–503

DOI: 10.1007/s11606-009-1240-1

© Society of General Internal Medicine 2010

INTRODUCTION

Clinical trials have demonstrated that effective treatment of hypertension can greatly reduce strokes and other cardiovascular events. Less is known regarding the impact of health services exposures in the real world. This study seeks to determine if antihypertensive medication adherence, ambulatory visits, and type of antihypertensive medication exposures are protective for stroke and death among hypertensive patients in the community.

Medication refill adherence calculated using pharmacy records is a well-validated measure of medication adherence^{1–4} and has been suggested as an important quality measure for hypertension care.^{1,5} Some studies have tied low adherence to increases in costs or hospitalizations,^{6–8} but previous studies have not documented an association between adherence and major clinical outcomes.^{9,10} Only one recent case-control study has demonstrated an association between antihypertensive medication adherence and incidence of cerebrovascular disease.¹¹ We hypothesized that medication refill adherence would help protect chronic hypertensive patients from stroke and death.

Well-controlled studies have generally demonstrated that routine ambulatory visits do not have protective effects for the chronically ill.^{12–14} The most notable previous study of the impact of ambulatory visits focused on patients with chronic diseases that often require hospitalization for whom increased surveillance might be expected to increase hospitalization rates.¹² Hypertension seldom leads to hospitalization, and ambulatory visits for uncomplicated hypertension are typically employed to assess and improve blood pressure control. So, we hypothesized that ambulatory visits would help protect chronic hypertensive patients from stroke and death but presumed that the effect of ambulatory visits would be small.

We also hypothesized that thiazide diuretic and combination antihypertensive medication exposure would be associated

Data for this study were also used in the following Poster presentation. Academy Health, Washington DC, June 9, 2008. Bailey JE, Wan JY, Tang J, Ghani MA, Cushman WC. Antihypertensive medication adherence protects community dwelling hypertensive people from strokes and death.

Tang, J, Wan, JY, and Bailey, JE. Performance of comorbidity measures to predict stroke and death in a community-dwelling, hypertensive Medicaid population. *Stroke* 2008;39:1938–1944.

This research was supported by a grant from the American Heart Association.

Received June 10, 2009

Revised November 13, 2009

Accepted December 10, 2009

Published online February 18, 2010

with improved clinical outcomes since a large randomized clinical trial has demonstrated that thiazide-type diuretics are the most effective antihypertensives in decreasing risk of stroke.¹⁵ Also, numerous studies have demonstrated that use of fixed-dose combination medications improves adherence.¹⁶ This study employs a large administrative database to assess whether these easily measurable health services and medication utilization patterns are associated with the best clinical outcomes for hypertension.

METHODS

Design and Setting

This retrospective cohort study followed chronic medication-treated hypertensive individuals enrolled in Tennessee's Medicaid program (TennCare) for at least 3 continuous years from 1994 through 2000 inclusive. During the study period, TennCare enrollees generally experienced minimal barriers to medication and primary care access. All TennCare enrollees were assigned to a primary care provider whose contract required providing timely access to essential services. The TennCare pharmacy benefit required no co-pays, the formulary covered all major generic and non-generic hypertensive medications, and enrollees were able to obtain 1 month's supply of medication at a time. Administrative data and vital records served as primary data sources for the study. These data sources and relevant linkage procedures have been described previously.^{17,18}

Subjects

The hypertensive cohort was defined using eligibility, inpatient, professional, and pharmacy claims data. The cohort included all non-institutionalized persons with continuous eligibility (>320 days/year) for at least 3 years, lack of Medicare eligibility, age 18 to 64 in each study year, yearly diagnosis of hypertension, and receipt of at least one anti-hypertensive medication prescription for the two baseline years. Patients were excluded who died or had a stroke during their baseline 2-year period. Stroke was defined as any inpatient or professional claim including an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis code 430 to 438, thereby excluding virtually 100% of those with previous history of stroke.^{19–21} After the baseline period, eligible patients (n=49,479) were followed for a 1- to 5-year follow-up period in which study outcomes could occur.

Demographic variables were assessed using baseline period administrative demographic and eligibility files. Eligibility categories included: Medicaid only, disabled, uninsured (lacking insurance at program initiation), and uninsurable (deemed uninsurable because of preexisting conditions). Comorbidity was assessed using baseline and follow-up period inpatient and professional administrative data for paid claims.

Study Outcomes

The two primary study outcomes were time to stroke and time to death. ICD-9-CM codes defining stroke are shown in Table 1. Stringent requirements for stroke diagnosis following the recommendations of Reker and others²² were designed to maximize the positive predictive value and specificity of

Table 1. ICD-9-CM Diagnosis Codes Used to Define Outcome and Comorbidity Variables

Condition	Codes included	Codes excluded
Stroke	Subarachnoid or intracerebral hemorrhage: 430–431 ^a Cerebral infarction: 433.11, 433.21, 433.81, 433.91, 434.01, 434.11, 434.91 ^b Acute cerebrovascular disease: 436 ^b	Traumatic brain injury: 800–804, 850–854 ^b
Obesity	278.0 ^c	
Diabetes	250× in both baseline years ^c	
Mental illness	290–302, 306–319 ^c	
Substance abuse	303–305 ^c	
Hypercholesterolemia	272 ^c	
Congestive heart failure	402.01, 402.11, 402.91, 425–425.9, 428–428.9, 429.3 ^b	
Atrial fibrillation	427.31, 427.32 ^d	
Transient ischemic attack	435, 435.x ^c	
Myocardial infarction	410–412 ^b	

^aPrimary diagnosis on one or more inpatient claim

^bAny diagnosis from one or more inpatient claims

^cAny diagnosis from one or more inpatient or outpatient professional claims

^dAny diagnosis from one or more inpatient or two or more outpatient professional claims

diagnosis as described previously.¹⁷ Death was defined as all-cause mortality according to vital records.

Independent Variables

Demographic and comorbidity variables acted as control variables. Based on the literature review and our research, we selected the most promising alternative comorbidity measures to serve as additional control variables in the analyses.¹⁷ The following baseline comorbidity variables were included as defined in Table 1: (1) obesity, (2) diabetes, (3) mental illness, (4) substance abuse, and (5) hypercholesterolemia. Comorbidity variables in the follow-up period were calculated for every 6 months prior to event or study conclusion as defined in Table 1: (1) congestive heart failure, (2) atrial fibrillation, (3) transient ischemic attack, and (4) myocardial infarction. In addition, Charlson index was calculated for the baseline and follow-up as previously described.¹⁷ To avoid loss of statistical power due to collinearity among comorbidity variables, we limited consideration to individual comorbidities for which there was a priori evidence of strong associations with outcomes of interest. Previous research suggests that collinearity is much more likely to occur among comorbidity measures using individual conditions rather than between individual comorbidities and the Charlson index.¹⁷

Overall health care utilization is a marker of comorbidity and may predict clinical outcomes better than some diagnosis-based scores.²³ Our study assessed four independent interval health care utilization variables for the baseline period and for every 3 months in the follow-up period prior to the event or the

conclusion of the study: (1) ambulatory visits per year, (2) emergency visits per year, (3) hospital visits per year, and (4) hospital days per year.

Medication utilization was assessed with several validated measures using electronic pharmacy data. TennCare prescription data are accurate since electronic claims submission occurs at point of service.¹⁸ Levels of antihypertensive medication utilization are known to be associated with severity of illness and level of comorbidity since these medications are used to treat a variety of cardiovascular and other conditions in addition to hypertension.^{24,25}

Using the general method proposed by Steiner et al.,^{1,26} we calculated the following nine medication utilization variables for each subject for the baseline period and for every 6-month period in the follow-up period prior to an outcome event or the conclusion of the study: Antihypertensive Variety Exposure defined as the number of drug classes filled ever; Antihypertensive Regimen Complexity defined as the number of drug classes filled per month; Antihypertensive Medication Refill Adherence; Antihypertensive Medication Exposure defined as percentage of days in the time period with a filled prescription for each of the four major classes [thiazide-type diuretic, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (ACEI/ARB), calcium channel blocker (CCB), and beta adrenergic blocker (BB)]; Combination Medication Exposure defined as the percentage of days with a combination prescription filled; Aspirin Exposure defined as the percentage of days with an aspirin prescription filled.

Medication Refill Adherence (MRA) was calculated as the percentage of eligible prescription days filled (total days' supply for all qualifying drug classes/total number of days from the first to the last fill in the interval $\times 100$, capped at 100%) for all antihypertensive medications taken in the time period. MRA was capped at 100% because, given the absence of prior literature indicating that hypertensive medication oversupply has significant impact on stroke and death, we were solely interested in the impact of undersupply on these outcomes. MRA was calculated for each individual for all qualifying antihypertensive drugs for the period of interest. For example, an individual on two drugs during the first 6-month (180 day) follow-up period, receiving 180 days' supply for drug one and only 90 days' supply for drug two, would have an MRA of 75%. MRA was assessed for each individual for the 2-year baseline period and every 6 months in the follow-up period. MRA produces identical results for adherence as the similarly calculated medication possession ratio and has been well validated in numerous studies as an accurate measure of adherence.¹⁻⁴

Analysis

Cox regression modeling determined bivariate and multivariate associations with time to event (death and stroke) to produce hazard ratios (HR) using standard methods.²⁷ Multivariate modeling employed a stepwise procedure with all the independent variables in the Cox model. Hazard ratios and confidence intervals (CI) were computed in SAS using PHREG procedure with a MULTIPASS statement in order to reduce the consumption of computing resource.²⁸

Variables with $p < 0.05$ from the stepwise procedure were deemed significant. Hazard ratios for MRA were calculated for a 15% difference in adherence in order to assist with interpretation

since this difference approximately corresponds to a change in adherence by one pill per week for a once-a-day regimen.

Following the above analyses, the baseline MRA variable was used to categorize all subjects as either adherent or non-adherent using an 80% cutoff following Chapman's criteria.²⁹ The log-log survival plots showed that the adherent and non-adherent groups were not proportional. Thus, adjusted Kaplan-Meier survival curves were estimated using the direct adjusted method based on the stratified Cox regression model.³⁰ Both dichotomous and continuous variables were directly used to create adjusted survival curves that average the estimated survival curves for each patient. Five-year survival probabilities were produced for the adherent and non-adherent groups.

In order to test the difference in survival between two adherence groups, the adjusted number of events for each group was calculated from the adjusted survival probability.³¹⁻³³ Because the estimates are based on the actual counts that are not continuous with the normal approximation, the Yates correction for z-test was applied.²⁸ The null hypothesis for the comparison is that the two adherence levels have the same effect on survival. The null hypothesis is rejected if the p-value of z-test is less than 0.05.

RESULTS

Patients

We followed 49,479 subjects retrospectively during the period 1994–2000 for an average total observation period of 4.7 years, including the 2-year baseline period. Baseline characteristics of the study population are shown in Table 2. Mean age for study subjects was 48.5 years. Wide variations in levels of comorbidity were noted with Charlson Index values ranging from 0 to 16 with a mean Charlson Index of 1.71.

Health Care and Medication Utilization

At baseline, subjects had a mean of 5.2 ambulatory visits, 0.6 emergency visits, 1.0 hospital visits, and 4.9 hospital days per year (Table 3). Health care utilization varied widely, and the distributions for levels of utilization were highly skewed with ambulatory visits ranging from 0 to 86.5 per year in the baseline period.

The average variety exposure for subjects was 2.3 different classes of antihypertensive medications during the baseline period. The average regimen complexity for subjects was more than one antihypertensive medication regularly (1.04) and, for some subjects, as many as 5.8 classes of antihypertensive prescriptions filled regularly. Mean MRA was 67% and ranged from 3% to 100%.

Hazards of Stroke and Death

Among the 49,479 subjects who met study criteria, 619 strokes (1.25%) and 2,051 deaths (4.15%) occurred during an average follow-up period of 2.7 years. The 49,479 study subjects contributed 133,593 person-years of patient follow-up time with an actual stroke rate of 4.6 strokes per 1,000 person-years. Bivariate associations with stroke and death are shown in Table 4. In the baseline and follow-up periods, most

Table 2. Baseline Characteristics of Hypertensive Patients in Study

Characteristics	No. (%) ^a n=49,479
Gender	
Male	15,974 (32.28)
Female	33,504 (67.71)
Race	
Black	13,829 (27.95)
White	33,048 (66.79)
Other	245 (0.50)
Eligibility status	
Medicaid only	4,864 (9.83)
Disability	18,244 (36.87)
Uninsured	19,278 (38.96)
Uninsurable	7,091 (14.33)
Urban/rural status	
Urban	20,338 (41.10)
Greater metropolitan area	7,931 (16.03)
Rural	20,747 (41.93)
Geographic region	
East Tennessee	19,328 (39.06)
Middle Tennessee	15,012 (30.34)
West Tennessee	14,676 (29.66)
Managed care organization type	
Statewide	32,088 (64.85)
Regional	17,389 (35.14)
Comorbidity	
Diabetes diagnosis in both years of run-in	2,290 (4.63)
Obesity	3,048 (6.16)
Mental illness	12,142 (24.54)
Substance abuse	4,149 (8.39)
Congestive heart failure	1,737 (3.51)
Atrial fibrillation	706 (1.43)
Transient ischemic attack	608 (1.23)
Myocardial infarction	2,256 (4.56)
Hypercholesterolemia	8,793 (17.77)
Comorbidity	Mean (range)
Charlson Index	1.71 (0–16)
Other demographic variables	
Age (years)	46.5 (18–62)
Follow-up period (years eligible)	2.66 (0.005–5.00)
Socioeconomic status	Median (range)
Income of county of residence in 1998	\$3,483 (\$19,760–\$69,104)

^aNumbers do not add up to total and percents do not add up to 100 because of non-responses

comorbidities and types of health care utilization were associated with increased bivariate hazards of stroke and death. Likewise, higher levels of medication utilization generally were associated with increased bivariate hazards of stroke and death. The major exception to this general pattern was for thiazide exposure, which was associated with decreased bivariate hazards of stroke and death.

In the multivariate analysis (Table 5), urban residence was independently associated with increased hazards of stroke (HR 1.25; CI 1.03–1.51) and death (HR 1.19; CI 1.07–1.32). Increases in health care utilization in the baseline and follow-up periods still were generally associated with increased hazards of stroke and death. In contrast, in the multivariate analysis, increases in baseline ambulatory visits were found to place subjects at decreased hazards of death (HR 0.99; CI 0.98–1.00) as did baseline emergency visits (HR 0.97; CI 0.94–1.00).

After controlling for potential confounding factors, we found MRA to be strongly protective for stroke and death (Table 5). Adherence at baseline was associated with decreased multivariate hazards of stroke (HR 0.91; CI 0.86–0.97). Adherence in the follow-up period was associated with decreased multivariate hazards of both stroke (HR 0.92; CI 0.87–0.96) and death (HR

0.93; CI 0.90–0.96). These associations were similar in magnitude when other medication exposures were not included in the multivariate models for stroke and death (data not shown).

Exposure in the follow-up period to an increased variety of antihypertensive medication was independently associated with a 31% increased hazard of stroke (CI 1.21–1.42) and a 15% increased hazard of death (CI 1.09–1.21), but higher levels of exposure to thiazide, ACEI/ARB, CCB, and BB were associated with 3–4% decreased hazards of death (Table 5). Exposure to combination antihypertensive medication was not independently associated with decreased hazards of stroke or death in either the baseline or follow-up period. Aspirin exposure was independently associated with 3% decreased hazards of death (CI 0.94–1.00) in the follow-up period. In multivariate analysis baseline thiazide exposure was independently associated with a 5% decreased hazard of death (CI 0.92–0.98). Exposure to thiazide in the follow-up period was independently associated with an 11% decreased hazard of stroke (CI 0.85–0.93) and 4% decreased hazard of death (CI 0.93–0.99).

Survival Analysis

Using the 80% cutoff criteria,²⁹ 60.6% of subjects were classified as non-adherent at baseline. The adjusted Kaplan-Meier survival curves (Fig. 1) demonstrate that ≥80% baseline refill adherence is associated with better 5-year estimated survival than <80% refill adherence for death outcome ($P<0.001$) and for a combined outcome of stroke or death ($P<0.001$). The adjusted survival curves for stroke were not significantly different ($P=0.262$; $P=0.248$ after Yates correction). Based on the survival model, the probability of survival at the end of 5 years was 0.938 for the

Table 3. Baseline Health Care and Medication Utilization

Health care utilization	Mean (range)
Baseline period health care utilization	
Ambulatory visits per year	5.2 (0–86.5)
Emergency visits per year	0.6 (0–66)
Hospital visits per year	1.0 (0–13)
Hospital days per year	4.9 (0–327)
Baseline medication utilization	
Antihypertensives	
Variety exposure (no. of drug classes filled ever)	2.33 (1–8)
Regimen complexity (no. of drug classes filled regularly)	1.04 (0.03–5.84)
Refill adherence (% of eligible prescription days filled)	67 (3–100)
Thiazide diuretic exposure	
% subjects with prescription filled	49.9
% of days thiazide diuretic filled	19 (0–100)
ACE inhibitor/ARB exposure	
% subjects with prescription filled	56.2
% of days ACE inhibitor/ARB filled	17 (0–100)
Calcium blocker exposure	
% subjects with prescription filled	52.5
% of days calcium blocker filled	26 (0–100)
Beta blocker exposures	
% subjects with prescription filled	31.1
% of days beta blocker filled	14 (0–100)
Combination medication exposure	
% subjects with prescription filled	5.1
% of days combination filled	1.77 (0–100)
Other medications	
Aspirin exposure	
% subjects with prescription filled	8.7
% of days aspirin filled	2.82 (0–100)

Table 4. Bivariate Results for Stroke and Death Outcomes

Characteristics	Stroke hazard ratio (95% CI)	Death hazard ratio (95% CI)
Demographic characteristics		
Age	1.06 (1.05–1.07) ^a	1.06 (1.05–1.07) ^a
Male gender	0.93 (0.78–1.11)	1.61 (1.47–1.76) ^a
Black race	1.69 (1.43–1.99) ^a	1.13 (1.06–1.93) ^a
Median income for county ^b	1.02 (1.01–1.03) ^a	1.01 (1.01–1.02) ^a
Eligibility status		
Medicaid only	1.00	1.00
Disabled	2.45 (1.76–3.42) ^a	3.54 (2.88–4.36) ^a
Uninsured	0.97 (0.68–1.39)	1.07 (0.85–1.34)
Uninsurable	1.02 (0.66–1.59)	1.17 (0.90–1.54)
Urban/rural status		
Rural	1.00	1.00
Metropolitan	0.79 (0.60–1.04)	1.03 (0.90–1.18)
Urban	1.44 (1.22–1.71) ^a	1.31 (1.20–1.44) ^a
Geographic region		
East Tennessee	1.00	1.00
Middle Tennessee	1.33 (1.09–1.62) ^a	1.11 (1.00–1.24) ^a
West Tennessee	1.56 (1.29–1.89) ^a	1.08 (0.97–1.20)
Managed care organization type		
Statewide	1.00	1.00
Regional	0.98 (0.83–1.16)	1.03 (0.94–1.13)
Health care utilization in baseline period		
Ambulatory visits	1.01 (0.99–1.02)	1.02 (1.02–1.03) ^a
Emergency visits	1.06 (1.03–1.08) ^a	1.08 (1.07–1.09) ^a
Hospital visits	1.38 (1.32–1.46) ^a	1.49 (1.46–1.52) ^a
Hospital days	1.01 (1.01–1.02) ^a	1.02 (1.02–1.02) ^a
Health care utilization in previous quarter		
Ambulatory visits	1.05 (1.03–1.08) ^a	1.07 (1.06–1.08) ^a
Emergency visits	1.13 (1.09–1.17) ^a	1.17 (1.15–1.18) ^a
Hospital visits	2.02 (1.77–2.31) ^a	3.12 (3.01–3.24) ^a
Hospital days	1.05 (1.03–1.06) ^a	1.07 (1.07–1.07) ^a
Comorbidity in baseline period		
Obesity	0.75 (0.52–1.09)	1.08 (0.90–1.28)
Diabetes	2.42 (1.90–3.08) ^a	2.44 (2.13–2.78) ^a
Mental illness	0.93 (0.78–1.12)	1.22 (1.11–1.34) ^a
Substance abuse	1.57 (1.23–2.00) ^a	2.50 (2.23–2.80) ^a
Hypercholesterolemia	0.92 (0.82–1.04)	0.98 (0.79–1.21)
Charlson Index	1.17 (1.13–1.21) ^a	1.41 (1.39–1.43) ^a
Comorbidity in previous 6 months		
Charlson Index	1.47 (1.38–1.56) ^a	1.84 (1.80–1.88) ^a
Congestive heart failure	5.79 (4.26–7.87) ^a	11.35 (9.98–12.90) ^a
Atrial fibrillation	3.37 (2.08–5.46) ^a	6.33 (5.19–7.72) ^a
Transient ischemic attack	5.93 (3.75–9.37) ^a	2.89 (2.04–4.10) ^a
Myocardial infarction	2.62 (1.62–4.24) ^a	3.87 (3.11–4.82) ^a
Baseline medication utilization		
Antihypertensives		
Variety exposure (no. of drug classes filled ever)	1.28 (1.20–1.36) ^a	1.23 (1.19–1.28) ^a
Regimen complexity (no. of drug classes filled regularly)	1.13 (1.00–1.27) ^a	1.33 (1.25–1.41) ^a
Refill adherence (% of eligible prescription days filled) ^c	0.96 (0.91–1.01)	1.04 (1.01–1.06) ^a
Thiazide diuretic exposure (% of days filled) ^c	0.92 (0.88–0.96) ^a	0.89 (0.87–0.91) ^a
ACE inhibitor/ARB exposure (% of days filled) ^c	0.98 (0.94–1.02)	1.02 (1.00–1.04) ^a
Calcium blocker exposure (% of days filled) ^c	1.07 (1.04–1.11) ^a	1.05 (1.03–1.07) ^a
Beta blocker exposure (% of days filled) ^c	0.96 (0.92–1.01)	0.97 (0.95–1.00) ^a
Combination drug exposure (% of days filled) ^c	1.03 (0.92–1.14)	0.98 (0.92–1.05)
Aspirin exposure (% of days aspirin filled) ^c	1.20 (1.12–1.29) ^a	1.19 (1.15–1.24) ^a
Medication utilization in previous 6 months		
Antihypertensives		
Variety exposure (no. of drug classes filled ever)	1.32 (1.24–1.41) ^a	1.29 (1.24–1.34) ^a
Regimen complexity (no. of drug classes filled regularly)	1.13 (1.03–1.23) ^a	1.11 (1.06–1.16) ^a
Refill adherence (% of eligible prescription days filled) ^c	0.98 (0.94–1.01)	0.97 (0.95–0.99) ^a
Thiazide diuretic exposure (% of days thiazide filled) ^c	0.88 (0.85–0.92) ^a	0.89 (0.87–0.91) ^a
ACE inhibitor/ARB exposure (% of days ACE inhibitor/ARB filled) ^c	0.99 (0.96–1.01)	0.98 (0.96–0.99) ^a
Calcium blocker exposure (% of days calcium blocker filled) ^c	1.04 (1.01–1.07) ^a	1.01 (0.99–1.02)
Beta blocker exposure (% of days beta blocker filled) ^c	0.99 (0.95–1.02)	0.97 (0.95–0.99) ^a
Combination medication exposure (% of days combination filled) ^c	0.99 (0.89–1.10)	0.99 (0.93–1.05)
Aspirin exposure (% of days aspirin filled) ^c	1.10 (1.05–1.15) ^a	1.09 (1.06–1.11) ^a

^a Significant *P*-value (*P* < 0.05)^b 1 unit = \$1,000^c 1 unit = 15% change

Table 5. Multivariate Results for Stroke and Death Outcomes

Characteristics	Stroke hazard ratio (95% CI) ^a	Death hazard ratio (95% CI) ^a
Demographic characteristics		
Age	1.06 (1.04–1.07)	1.05 (1.04–1.06)
Male gender	NS	1.55 (1.40–1.70)
Black race	1.50 (1.23–1.83)	NS
Median income for county ^b	NS	1.01 (1.00–1.02)
Eligibility status		
Disabled	1.77 (1.48–2.11)	1.67 (1.50–1.85)
Uninsured	NS	NS
Uninsurable	NS	NS
Geographic region		
Middle	NS	NS
West	NS	1.16 (1.05–1.30)
Urban/rural status		
Metropolitan	NS	NS
Urban	1.25 (1.03–1.51)	1.19 (1.07–1.32)
Managed care organization type		
Regional	NS	NS
Health care utilization in baseline period		
Ambulatory visits	NS	0.99 (0.98–1.00)
Emergency visits	NS	0.97 (0.94–1.00)
Hospital visits	1.21 (1.12–1.30)	1.09 (1.04–1.14)
Hospital days	NS	1.01 (1.00–1.01)
Health care utilization in previous quarter		
Ambulatory visits	NS	NS
Emergency visits	1.08 (1.01–1.15)	1.10 (1.07–1.14)
Hospital visits	1.22 (1.02–1.47)	1.48 (1.39–1.58)
Hospital days	NS	1.04 (1.03–1.04)
Comorbidity in baseline period		
Obesity	0.57 (0.38–0.85)	0.76 (0.63–0.92)
Diabetes	NS	NS
Mental illness	NS	NS
Substance abuse	NS	1.46 (1.28–1.66)
Hypercholesterolemia	NS	0.81 (0.71–0.92)
Charlson Index	NS	1.18 (1.16–1.21)
Comorbidity in previous 6 months		
Charlson Index	1.19 (1.10–1.28)	1.29 (1.25–1.33)
Congestive heart failure	1.53 (1.06–2.22)	1.45 (1.23–1.71)
Atrial fibrillation	NS	NS
Transient ischemic attack	3.89 (2.42–6.25)	NS
Myocardial infarction	NS	0.75 (0.59–0.96)
Baseline medication utilization		
Antihypertensives		
Variety exposure (no. of drug classes filled ever)	NS	NS
Regimen complexity (no. of drug classes filled regularly)	NS	1.17 (1.08–1.27)
Refill adherence (% of eligible prescription days filled) ^c	0.91 (0.86–0.97)	NS
Thiazide diuretic exposure (% of days thiazide filled) ^c	NS	0.95 (0.92–0.98)
ACE inhibitor/ARB exposure (% of days ACE inhibitor/ARB filled) ^c	NS	NS
Calcium blocker exposure (% of days calcium blocker filled) ^c	1.05 (1.01–1.10)	NS
Beta blocker exposure (% of days beta blocker filled)	NS	NS
Combination medication exposure (% of days combination filled)	NS	NS
Aspirin exposure (% of days aspirin filled)	NS	NS
Previous 6 month medication utilization		
Antihypertensives		
Variety exposure (no. of drug classes filled ever)	1.31 (1.21–1.42)	1.15 (1.09–1.21)
Regimen complexity (no. of drug classes filled regularly)	NS	NS
Refill adherence (% of eligible prescription days filled) ^c	0.92 (0.87–0.96)	0.93 (0.90–0.96)
Thiazide diuretic exposure (% of days thiazide filled) ^c	0.89 (0.85–0.93)	0.96 (0.93–0.99)
ACE inhibitor/ARB exposure (% of days ACE inhibitor/ARB filled) ^c	NS	0.97 (0.95–0.99)
Calcium blocker exposure (% of days calcium blocker filled) ^c	NS	0.97 (0.95–0.99)
Beta blocker exposure (% of days beta blocker filled) ^c	NS	0.97 (0.95–0.10)
Combination medication exposure (% of days combination filled)	NS	NS
Aspirin exposure (% of days aspirin filled) ^c	NS	0.97 (0.94–1.00)

^aSignificant *P*-value (*P*<0.05)

NS, Not selected in final result

^b1 unit=\$1,000^c1 unit=15% change

Figure 1. Adjusted Kaplan-Meier survival curves for stroke (panel A), death (panel B), and stroke or death (panel C) according to overall level of antihypertensive medication refill adherence.

Medication refill adherence $\geq 80\%$	—
Medication refill adherence $< 80\%$	—

adherent group and 0.933 for the non-adherent group, resulting in a difference in the survival probability for death of 0.5% between the adherent and non-adherent groups.

DISCUSSION

The low rate of antihypertensive medication adherence in this statewide Medicaid population (39.4%) replicates the findings of other researchers in other insured populations.^{34,35} This study demonstrates that low antihypertensive medication adherence is a potent cardiovascular risk factor for community-dwelling hypertensive patients and that increasing adherence by just one pill per week for a once-a-day regimen (i.e., increasing MRA by 15%) can result in a 7% reduction in hazard of death or a number needed to treat (NNT) of 344 to prevent one death in 2.7 years. This compares very favorably with the NNT estimated at greater than 500 for cholesterol-lowering therapy to prevent one death in 5 years for patients with two or more risk factors such as hypertension.^{15,36}

This study demonstrates that medication adherence, a factor very amenable to change, is among the most important cardiovascular risk factors for hypertensive patients. We found a 0.5% increase in deaths over 5 years attributable to non-adherence (MRA < 80%). Given that there are approximately 68 million US adults with hypertension³⁷ and approximately 60% are non-adherent by this standard, these results suggest that approximately 200,000 lives could be saved over the next 5 years by increasing adherence levels for all hypertensive patients to $\geq 80\%$. These estimates of the lives saved by improved adherence and control of hypertension are consistent with the estimates of other authors.^{37,38} It is likely that a similar number of strokes could be prevented through increases in adherence, but our study had insufficient stroke events and was underpowered to show significant impact on stroke in the survival analysis due in part to the stringent requirements for stroke diagnosis.

Of particular interest to generalist physicians is the finding that increased ambulatory care was associated with decreased mortality risk. This study, unlike previous studies of cohorts of patients with chronic disease,^{12–14} found that ambulatory visits were protective for death once we controlled for the impact of comorbidity. The most notable of previous studies to assess the impact of ambulatory care showed that recently hospitalized veterans with diabetes, chronic obstructive pulmonary disease, or congestive heart failure randomized to an intensive primary care intervention actually experienced higher readmission rates.¹² The results of our community-based observational study are reassuring and are consistent with the a priori expectation of primary care physicians that their outpatient efforts to control hypertension pay off. Although the effect size for ambulatory visits was small, this study is to our knowledge the first to give clear evidence that ambulatory visits in community settings are beneficial for hypertensive patients. This finding is striking since ambulatory visits are subject to confounding by indication; sicker people go to the doctor more. By using meticulous methods to control for the effects of comorbidity, the current study was able to unmask the impact of ambulatory care.

The effect of ambulatory care is likely mediated by increasing opportunities for measurement and improvement of hypertension control. The finding that baseline emergency care exposure was protective for death suggests that emergency visits may also provide important opportunities to identify and treat patients

with uncontrolled hypertension. Further research is needed to determine the optimal number and types of visits needed to maintain blood pressure control and prevent adverse events, the primary mechanisms through which ambulatory visits improve outcomes, and the most effective methods for improving adherence and control of hypertension in ambulatory settings.¹³

This study also demonstrated that exposures to most major classes of antihypertensives were protective for mortality independent of adherence levels. This is consistent with clinical trials and meta-analyses of hypertension outcome trials demonstrating similar mortality benefits for these major classes.³⁹ Only baseline CCB exposure was associated with increased risk of stroke, possibly because patients started on CCBs generally have more severe hypertension. Combination antihypertensive medication exposure was not independently associated with decreased risk of stroke or death.

The protective effects of thiazide-type diuretic exposure were most notable. Recent thiazide exposure decreased risk of stroke by 11%, the only medication exposure other than aspirin that was associated with decreased risk of stroke. Both baseline and recent thiazide use decreased risk of death. These impacts are particularly robust given that we controlled for exposure to other classes of medication, adherence, number of medications taken, and other well-validated measures of comorbidity. Our study is consistent with previous major randomized clinical trials and meta-analyses of antihypertensive therapy in showing that the lowest cost antihypertensive medications (thiazide-type diuretics) are lifesaving and prevent stroke.^{15,40,41}

The limitations of this study are inherent in the use of administrative data. Lack of access to clinical data prevented our measuring potential confounding variables such as severity of hypertension. However, the study has high external validity in that it fairly represents the health services exposures and clinical outcomes for a large population of patients with a very common condition. Although we had limited ability to measure and adjust for differences in comorbidity, we were able to employ well-validated methods for comorbidity adjustment of administrative data.¹⁷

The current study may have underestimated the effect of non-adherence by using a measure of adherence (i.e., MRA) that combines those who are adherent and those who receive an oversupply of antihypertensive medication from their pharmacy. Some recent studies indicate that oversupply may also be associated with non-adherence.^{42,43} Including the type of medication exposure variables in the same multivariate model with MRA may have further diluted the effect of adherence on stroke and death because of collinearity between these independent variables. Therefore, the effect of adherence demonstrated in this study likely represents a lower estimate than the true effect of adherence on stroke and death.

Healthy user bias could account for the unexpected protective effects of obesity for stroke and death, and hypercholesterolemia and history of myocardial infarction (MI) for death. Because coding forms have limited space for diagnoses, healthier patients are more likely to have stable chronic diagnoses listed as a code on the claim. So, the study's findings regarding obesity, hypercholesterolemia, and history of MI are probably explained by an administrative coding phenomenon. The study's generalizability is also potentially limited by its assessment of practice patterns 9 to 15 years ago. Although studies suggest that treatment of hypertension has become more aggressive since the late 1990s,

there have been no major changes in treatment guidelines or medication copayments for Medicaid patients since that period. These results cannot be generalized to older Medicare patients since they were not included in the study.

This study suggests that MRA can be used by primary care physicians at the point of care to recognize, track, and improve adherence and save lives. This research supports making MRA information readily available through electronic medical records to providers to help them support patient adherence. The study also supports clinical trial evidence and US guideline recommendations supporting frequent use of thiazide-type diuretics in the management of hypertension. In summary, adherence serves as a key mediator of risk of premature stroke and death that is amenable to action, and the best place for action is in the ambulatory setting.

Acknowledgments: This research was supported by a grant from the American Heart Association. The authors gratefully acknowledge the assistance of the TennCare Bureau of the State of Tennessee, Catherine Lewis and Deborah Gibson for their substantial editorial assistance, Grant Somes, PhD, and Andy Bush, PhD, for their assistance with the study design and analysis plan, and William Pulsinelli, MD, for contributing his advice and content expertise on the design and implementation of the study.

Conflicts of Interest: Dr. James Bailey has received a grant from Novo Nordisk, Inc., for reporting on diabetes quality of care, 2006–2008.

Jun Tang has been employed by Accredo Health Group, Inc., since 2007.

Dr. William Cushman has consulted for Sanofi-Aventis, Bristol-Myers Squibb, Novartis, Pfizer, Daiichi Sankyo, Forest, King Pharmaceuticals, Boehringer-Ingelheim, Roche, Takeda, Sciele, Pharmacopeia, and Gilead. He has received grants from Astra-Zeneca, Sanofi-Aventis, King, GlaxoSmithKline, and Novartis. He has a grant request pending with GlaxoSmithKline.

Corresponding Author: James E. Bailey, MD, MPH; Division of General Internal Medicine, Department of Medicine, University of Tennessee Health Science Center, 956 Court Avenue, Coleman D222, Memphis, TN 38163, USA (e-mail: jeb@uthsc.edu).

REFERENCES

1. Steiner JF, Koepsell TD, Fihn SD, Inui TS. A general method of compliance assessment using centralized pharmacy records. Description and validation. *Med Care*. 1988;26(8):814–23.
2. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother*. 2006;40(7–8):1280–8.
3. Bailey JE, Lee MD, Somes GW, Graham RL. Risk factors for antihypertensive medication refill failure by patients under Medicaid managed care. *Clin Ther*. 1996;18(6):1252–62.
4. Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care*. 1999;37(9):846–57.
5. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487–97.
6. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care*. 2005;43(6):521–30.
7. Weiden PJ, Kozma C, Grogg A, Locklear J. Partial compliance and risk of rehospitalization among California Medicaid patients with schizophrenia. *Psychiatr Serv*. 2004;55(8):886–91.
8. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. An empirical basis for standardizing adherence measures derived from administrative claims data among diabetic patients. *Med Care*. 2008;46(11):1125–33.

9. **Wetzels GE, Nelemans P, Schouten JS, Prins MH.** Facts and fiction of poor compliance as a cause of inadequate blood pressure control: a systematic review. *J Hypertens.* 2004;22(10):1849–55.
10. **Richter A, Anton SE, Koch P, Dennett SL.** The impact of reducing dose frequency on health outcomes. *Clin Ther.* 2003;25(8):2307–35. discussion 6.
11. **Kettani FZ, Dragomir A, Cote R, et al.** Impact of a better adherence to antihypertensive agents on cerebrovascular disease for primary prevention. *Stroke.* 2009;40(1):213–20.
12. **Weinberger M, Oddone EZ, Henderson WG.** Does increased access to primary care reduce hospital readmissions? Veterans Affairs Cooperative Study Group on Primary Care and Hospital Readmission. *N Engl J Med.* 1996;334(22):1441–7.
13. **Ma J, Stafford RS.** Screening, treatment, and control of hypertension in US private physician offices, 2003–2004. *Hypertension.* 2008;51(5):1275–81.
14. **Fisher ES, Wennberg DE, Stukel TA, Gottlieb DJ, Lucas FL, Pinder EL.** The implications of regional variations in Medicare spending. Part 2: health outcomes and satisfaction with care. *Ann Intern Med.* 2003;138(4):288–98.
15. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA.* 2002;288(23):2998–3007.
16. **Connor J, Rafter N, Rodgers A.** Do fixed-dose combination pills or unit-of-use packaging improve adherence? A systematic review. *Bull World Health Organ.* 2004;82(12):935–9.
17. **Tang J, Wan JY, Bailey JE.** Performance of comorbidity measures to predict stroke and death in a community-dwelling, hypertensive Medicaid population. *Stroke.* 2008;39(7):1938–44.
18. **Ray WA.** Policy and program analysis using administrative databases. *Ann Intern Med.* 1997;127(8 Pt 2):712–8.
19. **Rosamond WD, Folsom AR, Chambless LE, et al.** Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke.* 1999;30(4):736–43.
20. **Benesch C, Witter DM Jr, Wilder AL, Duncan PW, Samsa GP, Matchar DB.** Inaccuracy of the International Classification of Diseases (ICD-9-CM) in identifying the diagnosis of ischemic cerebrovascular disease. *Neurology.* 1997;49(3):660–4.
21. **Leibson CL, Naessens JM, Brown RD, Whisnant JP.** Accuracy of hospital discharge abstracts for identifying stroke. *Stroke.* 1994;25(12):2348–55.
22. **Reker DM, Hamilton BB, Duncan PW, Yeh SC, Rosen A.** Stroke: who's counting what? *J Rehabil Res Dev.* 2001;38(2):281–9.
23. **Marini C, Baldassarre M, Russo T, et al.** Burden of first-ever ischemic stroke in the oldest old: evidence from a population-based study. *Neurology.* 2004;62(1):77–81.
24. **Chobanian AV, Bakris GL, Black HR, et al.** Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42(6):1206–52.
25. **Gil-Nunez AC, Vivancos-Mora J.** Blood pressure as a risk factor for stroke and the impact of antihypertensive treatment. *Cerebrovasc Dis.* 2005;20(Suppl 2):40–52.
26. **Steiner JF, Prochazka AV.** The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol.* 1997;50(1):105–16.
27. **Allison PD.** *Survival Analysis Using SAS: A Practical Guide.* Cary: SAS Institute, Inc; 1995.
28. SAS Institute. *Statistical Analysis System (SAS).* In. 9.1 ed. Cary, NC; 2003.
29. **Chapman RH, Benner JS, Petrilla AA, et al.** Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med.* 2005;165(10):1147–52.
30. **Zhang X, Loberiza FR, Klein JP, Zhang MJ.** A SAS macro for estimation of direct adjusted survival curves based on a stratified Cox regression model. *Comput Methods Programs Biomed.* 2007;88(2):95–101.
31. **Kaplan EL, Meier P.** Nonparametric estimation from incomplete observations. *J Amer Statist Assoc.* 1958;53:457–81.
32. **Vey N, Blaise D, Stoppa AM, et al.** Bone marrow transplantation in 63 adult patients with acute lymphoblastic leukemia in first complete remission. *Bone Marrow Transplant.* 1994;14(3):383–8.
33. **Xie J, Liu C.** Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Stat Med.* 2005;24(20):3089–110.
34. **Siegel D, Lopez J, Meier J.** Antihypertensive medication adherence in the Department of Veterans Affairs. *Am J Med.* 2007;120(1):26–32.
35. **Elliott WJ, Plauschnat CA, Skrepnek GH, Gause D.** Persistence, adherence, and risk of discontinuation associated with commonly prescribed antihypertensive drug monotherapies. *J Am Board Fam Med.* 2007;20(1):72–80.
36. Therapeutics Initiative: Evidence Based Drug Therapy. Do Statins have a role in primary prevention? In: *Therapeutics Letter*; 2003.
37. **Ong KL, Cheung BM, Man YB, Lau CP, Lam KS.** Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension.* 2007;49(1):69–75.
38. **Gu G, Burt VL, Paulose-Ram R, Yoon S, Gillum RF.** High blood pressure and cardiovascular disease mortality risk among US adults: the third National Health and Nutrition Examination Survey mortality follow-up study. *Ann Epidemiol.* 2008;18(4):302–9.
39. **Turnbull F.** Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet.* 2003;362(9395):1527–35.
40. **Psaty BM, Lumley T, Furberg CD, et al.** Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA.* 2003;289(19):2534–44.
41. **Beckett NS, Peters R, Fletcher AE, et al.** Treatment of hypertension in patients 80 years of age or older. *N Engl J Med.* 2008;358(18):1887–98.
42. **Stroupe KT, Teal EY, Tu W, Weiner M, Murray MD.** Association of refill adherence and health care use among adults with hypertension in an urban health care system. *Pharmacotherapy.* 2006;26(6):779–89.
43. **Thorpe CT, Bryson CL, Maciejewski ML, Bosworth HB.** Medication acquisition and self-reported adherence in veterans with hypertension. *Med Care.* 2009;47(4):474–81.