Effect of Patient Comorbidities on Filling of Antihypertensive Prescriptions

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Objectives: To evaluate the extent of patient failure to fill antihypertensive prescriptions and to test the hypothesis that the presence of noncardiovascular disease is negatively associated with filling an antihypertensive prescription, and, conversely, that the presence of cardiovascular disease is positively associated with filling an antihypertensive prescription.

Study Design: Cross-sectional.

Methods: We sampled prescriptions written for 327 African Americans aged ≥18 years. Patients were enrolled in a Medicaid managed care plan and treated in 6 primary care practices between January 1, 2003, and February 8, 2005. Prescription filling was defined as a match between a new or renewed electronic prescription and an insurance claim within the next 30 days. We assessed the association of comorbidity type with filling an antihypertensive prescription by using an adjusted logistic regression model that accounted for clustering of prescriptions within patients.

Results: Of 1742 antihypertensive prescriptions, 1309 (75.1%) were filled. Prescriptions written for persons with 5 or more noncardiovascular comorbidities were significantly more likely to be filled (adjusted odds ratio [OR], 1.59; 95% confidence interval [CI], 1.07 ± 2.36) versus those for persons with fewer noncardiovascular comorbidities. The presence of cardiovascular comorbidities was not associated with filling of an antihypertensive prescription (adjusted OR, 0.72; 95% CI, 0.45-1.14).

Conclusion: Many antihypertensive prescriptions were not filled. Different types of patient comorbidity may differentially impact prescription filling. Further studies should examine whether these results generalize to other populations.

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For author information and disclosures, see end of text.

Poor blood pressure control substantially increases the risk of ischemic heart disease and stroke.[1] Although effective treatment for hypertension improves clinical outcomes and reduces healthcare costs,[1-3] 30% to 50% of treated patients continue to have uncontrolled blood pressure.[4,5] Successful pharmacologic treatment of any medical condition requires patient cooperation in a multiple-step pathway that includes[6,7]: (1) keeping a scheduled appointment with a physician; (2) accepting a prescription for a medication; (3) filling the prescription at a pharmacy; (4) taking the medication as prescribed; (5) maintaining an adequate supply of the medication by refilling the prescription in a timely manner; and (6) returning to the physician for ongoing monitoring.

Most research on antihypertensive adherence has focused on the fourth and fifth steps in this pathway.[8] However, there is empirical research on factors affecting antihypertensive prescription filling. Previous research on prescription filling used patient self-report and, to our knowledge, no study has linked provider prescriptions for antihypertensive medication to paid claims.[9-14]

In this study, we examined antihypertensive prescription filling by African American patients treated in affiliated academic practices and enrolled in a single Medicaid managed care plan. We hypothesized that patients would commonly fail to fill their prescriptions, reflecting evidence that even under clinical trial conditions, between 30% and 50% of patients do not take medications as prescribed.[15] Further, we hypothesized that more noncardiovascular comorbidities (eg, arthritis) would focus patient attention away from hypertension and would therefore be associated with poor antihypertensive prescription filling.[16-19] Conversely, cardiovascular conditions (eg, heart attack or stroke) would be associated with increased antihypertensive prescription filling[20-22] because of greater patient concern about the effect of hypertension on these conditions. We also hypothesized that higher blood pressure and use of lipid-lowering therapy, factors related to cardiovascular risk management, would be positively associated with antihypertensive prescription filling.

METHODS

Patient Population

Our patient population consisted of a subset of a larger study of hypertensive primary care patients.[23] For

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the larger data set, we identified hypertensive adults (≥18 years old) with at least 3 visits to 6 primary care practices affiliated with an academic medical center in Philadelphia, Pennsylvania, between January 1, 2003, and February 8, 2005. Hypertension was defined as 1 or more of the following: (1) an *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) coded diagnosis of hypertension at 2 or more outpatient visits; (2) a diagnosis of hypertension at 1 visit with an elevated blood pressure measurement or an active antihypertensive prescription[24]; or (3) an elevated blood pressure measurement at 2 or more visits. For the purposes of this study, we limited the larger data set to Medicaid patients enrolled in a collaborating managed care plan. We further restricted the analysis to African American patients because fewer than 10% of plan enrollees were from other racial groups.

Medicaid patients in this plan have full prescription coverage. Each time an enrolled patient filled a prescription, a claim was filed with the plan. However, Medicaid enrollment is quite dynamic: patients enter and leave Medicaid managed care programs frequently. Therefore, we limited the sample to patients with at least 3 months of continuous coverage during the study period. To ensure that patients were enrolled throughout the time a prescription could be filled, we also required that patients have at least 30 days of enrollment after the date of the prescription.

Antihypertensive Medication Data

Our unit of analysis was an electronically generated prescription for a new or renewed antihypertensive medication during the study period. We linked claims only for medications that required the physician to provide a prescription. Prescriptions written by hand or called directly to a pharmacy were not included. Prescriptions fell into 1 of the following antihypertensive drug classes: beta-blockers, calcium channel blockers, thiazide or potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and all other antihypertensive medications (eg, alpha-blockers, vasodilators). Diuretics (such as furosemide) that act at the Loop of Henle and prescriptions written on an as-needed basis were not included because they are most commonly used for other medical conditions.

Dependent Variable

The outcome of interest, filling an antihypertensive prescription, was determined by matching the prescribed generic drug name with an insurance claim for the same generic drug. A 30-day time frame for filling was selected because the plan reimburses pharmacies for only a 30-day supply; if a patient waited more than 30 days to fill the prescription, he or she would have likely exhausted the supply of previous medications. Study practices rarely provide sample medication to patients because of a systemwide policy prohibiting their distribution.

Primary Independent Variables

From the electronic medical record used by the 6 primary care practices, we created a database that included demographics, insurance status, clinical diagnoses, selected physiologic measures (eg, blood pressure), selected laboratory tests (eg, low-density lipoprotein [LDL] cholesterol), and prescribed medications. Study patients' clinical conditions were defined from *ICD-9-CM* coded conditions at all inpatient and outpatient encounters. Cardiovascular comorbidities included diabetes, coronary artery disease, or coronary artery disease equivalent (ie, stroke, other cerebral vascular disease, peripheral vascular disease). Because of variability of *ICD-9-CM* codes used for renal insufficiency, we created a separate indicator, serum creatinine of >2 mg/dL, for this condition. Prescriptions were considered to be written for patients with cardiovascular disease if any of the previous cardiovascular diseases were present at the time that the prescription was generated.

We defined noncardiovascular comorbidities using Elixhauser's comorbidity measure supplemented with noncardiovascular conditions that appeared in more than 5% of all hypertensive patients in study practices. We included conditions that might not affect prognosis but could be a significant focus of ongoing care (eg, osteoarthritis, diarrhea or constipation, esophageal reflux/gastritis, headache, chronic sinusitis) and strategically integrated certain comorbidities (eg, various forms of cancer) that were grouped separately in the Elixhauser index. (For a list of included noncardiovascular comorbid conditions, see the **eAppendix**, available at **www.ajmc.com**.) Our final list included 28 conditions. The number of unrelated comorbidities was divided at the median of 4 to create a 2-level variable for analysis. Each prescription was then assigned a value for number of noncardiovascular conditions present at the time the prescription was generated.

Other Covariates

To determine the relationship between severity of hypertension and prescription filling, we identified the blood pressure recorded prior to the generation of each prescription. We then created a variable with the following categories: (1) stage 1 hypertension with both systolic and diastolic readings meeting the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluatoin, and Treatment of High Blood Pressure (JNC VI) criteria (ie, 130-159/85-99 mm Hg for those with coronary artery disease equivalent or diabetes, 140-159/90-99 mm Hg for those without those conditions)[24]; (2) stage 2 hypertension meeting JNC VI criteria (ie, either systolic blood

Table 1. Characteristics of Study Patients With Hypertension (N = 327)

Characteristic	No. (%)
Patient demographics	
Age, y	
18-50	150 (45.9)
>50	177 (54.1)
African American	327 (100.0)
Female	230 (70.3)
Clinical characteristics	
Comorbidities	
≥1 cardiovascular comorbidities	170 (52.0)
≥5 noncardiovascular comorbidities	142 (43.4)
Chronic renal insufficiency	59 (18.0)
Blood pressure control	
Controlled blood pressure	155 (47.0)
Stage 1 hypertension (both systolic and diastolic)	38 (11.6)
Stage 2 hypertension	48 (14.7)
Elevated diastolic blood pressure only	14 (4.2)
Elevated systolic blood pressure only	72 (22.0)
LDL cholesterol treatment	
LDL cholesterol at NCEP III target	85 (26.0)
High untreated LDL cholesterol	125 (38.2)
Treated LDL cholesterol	117 (35.8)
Other active antihypertensive medications	
0	50 (15.3)
1	118 (36.1)
2	96 (29.4)
≥3	63 (19.3)
Subclasses of other types of medications	
0-3	61 (18.7)
4-6	99 (30.3)
7-9	75 (22.9)
≥10	92 (28.1)
Cardiologist or nephrologist care	165 (50.5)
Specific antihypertensive medications, by prescription (N = 1742)	
Calcium channel blocker	342 (19.6)
Diuretic	458 (26.3)
Beta-blocker	306 (17.6)
Angiotensin-converting enzyme inhibitor	422 (24.2)
Angiotensin receptor blocker	148 (8.5)
Other antihypertensive medication	66 (3.8)

LDL indicates low-density lipoprotein; NCEP III, National Cholesterol Education Program Third Report.

pressure >159 mm Hg or diastolic blood pressure >99 mm Hg)[24]; (3) only elevated systolic blood pressure; or (4) only elevated diastolic blood pressure.

We also examined the treatment of LDL cholesterol with a prescribed hydroxymethyl glutaryl coenzyme A reductase inhibitor ("statin") because it might reflect patient receptiveness to cardiovascular risk reduction. Each prescription was assigned a value consistent with the patient's status at the time the prescription was generated, within 1 of the following categories: (1) statin therapy; (2) an LDL cholesterol measurement that meets the National Cholesterol Education Program Third Report (NCEP III) target without a statin (ie, LDL cholesterol <100 mg/dL for patients with diabetes, coronary artery disease, or coronary heart disease equivalent conditions, or <130 mg/dL for other patients)[25]; or (3) elevated LDL cholesterol according to NCEP III criteria without statin therapy.[25]

Other covariates included age, sex, care by cardiologist or nephrologist, number of antihypertensive medications, and number of subclasses of nonantihypertensive medications. All patient characteristics were prescription level: a value for a given patient characteristic depended on the value of that variable at the time the prescription was generated.

Statistical Analysis

Some patients included in the sample were written multiple prescriptions, but some had only 1 prescription. Therefore, we conducted our analysis using generalized estimating equations (GEEs), an adjusted logistic regression model that accounts for clustering of prescriptions within patients. This technique reduces the influence any single patient had on the results. Because there were 327 patients from practices with 210

providers, we did not create a model that was clustered by provider. We assumed an exchangeable correlation matrix for all GEE models and adjusted for key predictors (comorbidity, statin use, and severity of hypertension) and other covariates. All statistical analyses were performed using Stata statistical software, version 9 (StataCorp LP, College Station, TX).

The University of Pennsylvania's institutional review board approved the study.

RESULTS

Of 15,708 hypertensive patients followed at the study practices, 824 (5%) were African Americans enrolled in the managed care plan. This figure is consistent with the proportion (5%) of all patients in study practices who are enrolled in this plan. Of these hypertensive African American patients, 327 (40%) were enrolled in the Medicaid plan for at least 3 consecutive months and had at least 1 antihypertensive medication prescribed during a covered interval.

Of the study sample, 70% were female and most were more than 50 years old (Table 1). Half of the population had at least 1 cardiovascular comorbidity, and nearly half had 5 or more noncardiovascular comorbidities. Nearly half of the population had uncontrolled blood pressure, with 15% of patients having stage 2 hypertension. Of 242 patients eligible for lipid-lowering therapy, about half were prescribed a statin medication.

We identified 1742 new or renewed antihypertensive prescriptions written for these patients during the 25-month study

Table 2. Associations of Patient Characteristics With Antihypertensive Prescription Filling[a]

Characteristic	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Patient demographics		
Age 18-50 y	0.58 (0.38 ± 0.89)	0.58 (0.37 ± 0.91)
Women	1.14 (0.72 ± 1.80)	0.97 (0.6 ± 1.56)
Clinical characteristics		
Comorbidities		
≥1 cardiovascular comorbidities	1.02 (0.67 ± 1.55)	0.72 (0.45 ± 1.14)
≥5 noncardiovascular comorbidities	1.56 (1.08 ± 2.25)	1.59 (1.07 ± 2.36)
Chronic renal insufficiency	1.14 (0.68 ± 1.90)	1.24 (0.73 ± 2.12)
Blood pressure control		
Stage 1 hypertension (both systolic and diastolic)	1.16 (0.82 ± 1.64)	1.21 (0.84 ± 1.74)
Stage 2 hypertension	1.63 (1.15 ± 2.32)	1.72 (1.19 ± 2.49)
Elevated diastolic blood pressure only	0.66 (0.44 ± 1.00)	0.66 (0.42 ± 1.04)
Elevated systolic blood pressure only	1.15 (0.88 ± 1.49)	1.10 (0.83 ± 1.47)
LDL cholesterol treatment		
LDL cholesterol at NCEP III target	1.17 (0.77 ± 1.78)	1.20 (0.77 ± 1.86)
Treated LDL cholesterol	1.74 (1.16 ± 2.61)	1.74 (1.13 ± 2.70)
Other active antihypertensive medications		
0	1.12 (0.76 ± 1.65)	1.11 (0.75 ± 1.66)
2	1.13 (0.85 ± 1.51)	1.13 (0.84 ± 1.52)
≥3	0.92 (0.65 ± 1.28)	0.90 (0.63 ± 1.29)
Subclasses of other types of medications		
4-6	1.42 (0.99 ± 2.03)	1.46 (1.01 ± 2.11)
7-9	1.03 (0.70 ± 1.52)	1.12 (0.74 ± 1.70)
≥10	1.06 (0.70 ± 1.60)	1.11 (0.71 ± 1.74)
Cardiologist or nephrologist care	1.41 (0.97 ± 2.06)	1.07 (0.72 ± 1.60)

CI indicates confidence interval; LDL, low-density lipoprotein; NCEP III, National Cholesterol Education Program Third Report.
[a]Reference groups: age >50 years, male, controlled blood pressure, no cardiovascular comorbidity, 4 or fewer noncardiovascular comorbidities, untreated high LDL cholesterol, 1 current antihypertensive prescription, 0-3 subclasses of other medications, no specialist care.

Take-away Points

This cross-sectional study of patients in a Medicaid managed care plan was done to evaluate the extent to which patients filled antihypertensive prescriptions.

- Many antihypertensive prescriptions were not filled.
- Patients with cardiovascular comorbidities were not more likely to fill antihypertensive prescriptions than patients without these conditions.
- Antihypertensive adherence interventions should target patients with cardiovascular comorbidities to maximize the possible benefits of these medications.

period; 1309 (75.1%) of these were filled. Approximately one quarter of prescribed medications were ACE inhibitors, one quarter were diuretics, and approximately 20% were calcium channel blockers.

Both before and after adjustment, being age 50 years or younger was associated with 42% lower odds of filling an antihypertensive prescription (Table 2). Prescriptions written for patients with 5 or more noncardiovascular comorbidities were significantly more likely to be filled: there was a 59% increase in the adjusted odds of filling compared with antihypertensive prescriptions written for patients with fewer noncardiovascular comorbidities. The presence of cardiovascular comorbidities was not significantly associated with prescription filling. Prescriptions for patients with stage 2 hypertension[24] had a 72% increase in the adjusted odds of filling (P = .004) versus prescriptions for patients with controlled blood pressure. Prescriptions for patients prescribed a statin medication also showed a 74% increase in the adjusted odds of filling versus prescriptions for patients with elevated LDL cholesterol by NCEP III criteria[25] receiving no treatment (P = .01).

DISCUSSION

Consistent with our hypothesis, one quarter of prescriptions for antihypertensive medications were not filled by our study sample of Medicaid managed care primary care patients with full prescription coverage. These findings indicate that although medication cost is an adherence barrier that disproportionately affects patients with the lowest income,[26-31] this population's failure to fill antihypertensive prescriptions appears to be mediated by additional factors.

Contrary to our hypothesis, prescriptions for patients with 5 or more noncardiovascular conditions were significantly more likely to be filled than similar prescriptions written for patients with fewer noncardiovascular conditions.

Previous studies of medication adherence have shown that noncardiovascular comorbidities are associated with poor adherence to cardiovascular medications.[17-19,32] A recent study by Kerr et al also reported that diabetic patients with more non–diabetes-related comorbid conditions were less likely to prioritize diabetes self-management.[33] Our study's unexpected findings may be a result of our focus on antihypertensive prescription filling at the pharmacy, an aspect of antihypertensive adherence that has not been previously evaluated. The relationship between comorbidity and filling of antihypertensive prescriptions may differ from that of self-management or refill adherence. It is possible that patients taking many other medications are conditioned to fill prescriptions. However, we did not find an association between filling antihypertensive prescriptions and the number of other types of medications prescribed for a patient.

Also contrary to our hypothesis, antihypertensive prescriptions written for patients with coronary artery disease or other conditions that increase cardiovascular risk (eg, diabetes) were not more likely to be filled. These results differ from previous studies' reports that high-risk patients who take antihypertensive medications are more adherent to cardiovascular medications.[20-22] However, a study by Taira et al found that a history of coronary artery disease was associated with poorer antihypertensive adherence.[34] It is possible that specialists were prescribing antihypertensive medications different from those prescribed by the primary care provider, but this presupposes a significant lack of communication between providers. Additionally, we did not find an association between prescription filling and treatment by cardiologists or nephrologists. Some prescriptions may have been filled outside of the managed care plan. This population of Medicaid patients is very sensitive to cost, however, and these clinics do not stock sample medications, making out-of-plan filling unlikely.

Prescriptions for patients who had stage 2 hypertension were more likely to be filled than prescriptions for patients with well-controlled blood pressure. Patients with very elevated blood pressure at a visit may be more motivated to obtain prescribed medication because of either the physician's or the patient's concern. Additionally, prescriptions written for patients receiving concurrent statin therapy were more likely to be filled compared with prescriptions written for patients in whom high LDL cholesterol was untreated. This finding may support previous work that identifies differences in the health behaviors and characteristics of statin users. Because statin adherence has been shown to be associated with other health maintenance behaviors such as screening,[35,36] patients prescribed statin medications may be more motivated to fill medications in order to achieve blood pressure control. On the other hand, one study of concurrent antihypertensive and lipid-lowering therapy reported that

approximately one third of patients on either antihypertensive or lipid-lowering agents were nonadherent with at least 1 of these medications.[21]

This study has several limitations. We studied a relatively small sample of African American patients in a single managed care plan. Therefore, our results are not generalizable and power to detect associations between dependent and independent variables may be limited. We may have missed prescriptions that were filled but did not generate a claim within the managed care plan (such as patients who filled prescriptions at Veterans Administration pharmacies), but as previously noted, we expected out-of-plan filling to be very limited. We did not attempt to link and therefore cannot quantify the number of prescriptions that were not written electronically, but calling prescriptions to pharmacies or hand-writing prescriptions is strongly discouraged in these practices. Because there are 210 physicians in these practices and we sampled 327 patients, we were unable to create models with provider clustering and were therefore unable to examine whether there were physician-level effects. We used *ICD-9-CM* diagnosis codes to define comorbidity. It is unknown whether *ICD-9-CM* coding detects cardiovascular and noncardiovascular conditions differentially, so we cannot speculate whether there was comorbidity detection bias that influenced our results.

Patient adherence to medication is a major challenge facing physicians today, and filling an antihypertensive prescription at a pharmacy is a key step in the adherence process. We found that a substantial portion of antihypertensive prescriptions were not filled, and prescriptions written for patients with increased cardiovascular risk were not more likely to be filled. These results raise warning flags for physicians and insurers. Physicians should be attentive to querying patients about which prescriptions they have filled and should preferably ask patients to bring prescription bottles to visits to facilitate review of the patient's and the physician's list of medications. All patients, but particularly those patients facing increased cardiovascular risk, should be targeted with messages that reinforce the need to obtain and take antihypertensive medications if we wish to close the gap between potential and realized improvement in patient health.

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