ABSTRACT

OBJECTIVE: To compare the persistence and compliance in a usual-care setting with 3 drugs (amlodipine, lisinopril, or valsartan) from 3 different pharmaceutical classes—calcium-channel blocker, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker, respectively, commonly used to treat hypertension.

METHODS: This retrospective observational study included a cohort of 142,945 continuously benefit-eligible patients from a pharmacy benefit manager drug claims database who began therapy with lisinopril, valsartan, or amlodipine. Concurrent use of other cardiovascular medications was assessed as a proxy for cardiovascular disease severity. Chronic Disease Score (CDS), derived from pharmacy claims data, was used to classify patient chronic disease burden as mild, moderate, or severe. Drug utilization measures included compliance, persistence, medication possession ratio (MPR), duration of therapy, and drug discontinuation. Multiple linear regression techniques were used to assess the impact of various predictor variables on study outcomes and to compare compliance among treatment groups, adjusted for age, gender, and CDS.

RESULTS: The mean age of the study cohort was 63.1 years; 53% were female. Just over one half (51%, n=73,148) received amlodipine, 28% (n=40,238) received lisinopril, and 21% (n=29,669) received valsartan. Significantly more valsartan patients (63%) remained persistent on therapy at 12 months past the index date of the first prescription, compared with amlodipine (53%) and lisinopril (50%) patients (P <0.001). Both crude and adjusted compliance rates also were greatest for valsartan patients, reflected by an adjusted mean MPR of 75%, compared with 67% for amlodipine and 65% for lisinopril (P <0.0001, both comparisons).

CONCLUSION: These results suggest that, in a usual-care setting, patients receiving valsartan (relative to amlodipine or lisinopril) appear to be more compliant and persistent with pharmacologic therapy, independent of patient chronic disease burden.

KEYWORDS: Antihypertensive therapy, Chronic Disease Score, Compliance, Persistence, Valsartan

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Hypertension is a chronic, asymptomatic disease affecting an estimated 25% of the U.S. adult population. It is associated with significant morbidity and mortality as well as considerable consumption of health care resources. Numerous clinical studies have shown that continuous control of arterial blood pressure improves outcomes. Approximately 30% of individuals with hypertension are unaware of their disease status; furthermore, 11% of those diagnosed are untreated, and 58% of those who are treated are not controlled.

Pharmacologic management of hypertension commonly involves the use of multiple therapeutic agents from several classes, including calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, diuretics, and the more recently introduced angiotensin receptor blockers (ARBs). Despite the overwhelming clinical evidence supporting improved outcomes with antihypertensive therapy, compliance and persistence remain poor, as evidenced by high medication discontinuation rates during the first year of therapy.

Medication tolerability problems, such as cough, swelling of the extremities, and fatigue, are associated with the chronic use of many antihypertensive agents. An unfavorable tolerability profile may be an important contributor to poor patient compliance. The ARBs have demonstrated excellent tolerability, with few side effects reported in placebo-controlled trials. In clinical trials, the ARB valsartan demonstrated comparable efficacy to the ACE inhibitors lisinopril and enalapril, with reduced incidence of cough. The side-effect rate for patients treated with the ARB valsartan was lower than that for patients treated with ACE inhibitors or CCBs. In addition, recent data suggest that ARBs are associated with improved patient persistence compared with ACE inhibitors, CCBs, diuretics, and beta-blockers.

Objective

The objective of this study was to assess patient compliance and persistence with the ARB valsartan (Diovan, Novartis) compared with that of representative agents from 2 other antihypertensive drug classes, the ACEI lisinopril (Zestril or Prinivil) and the CCB amlodipine (Norvasc). Compliance and persistence were assessed in a usual-care setting, where conditions generally differ considerably from those in controlled clinical trials. We hypothesized that patients using valsartan would be more compliant and persistent compared to patients using an ACEI or a CCB.

Methods

Cohort Construction

This was a retrospective, longitudinal cohort study utilizing an administrative pharmacy claims database from a large pharma-
cy benefits manager (PBM) providing benefits to more than 60 million drug-insured Americans. The information warehouse of this PBM is a demographically and geographically diverse database that contains 3 years of longitudinal pharmacy claims data representing the payer mix in the U.S. health care market, including drug-insured lives from health care insurance carriers, managed care organizations, employers, and retirement and government plans.

Members whose pharmacy claims data were available for research purposes were identified (N=46 million). Subjects who were continuously benefit-eligible for both mail-order and community pharmacy prescriptions between August 1, 1997, and July 31, 2000, were identified for preliminary cohort inclusion (n=14.6 million). From this population, the study cohort was identified, consisting of patients who received an initial prescription for valsartan, lisinopril, or amlodipine between August 1, 1998, and July 31, 1999. The study cohort represented patients who were new to therapy within the therapeutic class. Patients who received a prescription for a drug from the same class as the index agent during the 12 months preceding the index prescription were excluded from the cohort. The final study cohort was comprised of 142,945 patients.

All utilization analyses were performed relative to the index agent. The study evaluation included patient data for the 2-year period from August 1, 1998, through July 31, 2000, with each patient contributing 12 months of data following initiation of therapy with the index antihypertensive prescription.

### Study Definitions

Study definitions are provided in Figure 1. The “index prescription” was defined as each patient's first prescription during the study identification period, between August 1, 1998, and July 31, 1999. Patient age was calculated as of the date of the index prescription fill.

The drug utilization parameters that were evaluated included compliance, persistence, medication possession ratio (MPR), duration of therapy, and drug discontinuation. Compliance was calculated for all patients with at least 2 fills of the index antihypertensive agent. Compliance estimates were determined by summing the days’ supply (the number of days the dispensed drug supply should last based on prescriber dosing instructions) for all member prescriptions dispensed from the index prescription date to the last fill date (excluding the days’ supply dispensed at the last fill) divided by the patient’s duration of therapy. Duration of therapy was calculated as the last prescription date within the study window minus the index prescription date. The MPR was defined as the percentage of time that a patient had a supply of the index drug available during the 12 months following the index prescription, based on prescriber dosage instructions and days’ supply of medication dispensed at each fill. A patient may demonstrate high compliance but a lower MPR if that patient discontinues therapy at some point within the 12 months postinitiation of therapy, since the compliance calculation uses each patient’s specific length of drug therapy in days (i.e., the last fill date minus the first fill date) as the denominator, while the MPR calculation uses a fixed denominator of 365 days.

Discontinuation was characterized as stopping therapy with the index antihypertensive agent and not receiving a fill for the index agent within 60 days after exhausting the drug supply from the prior prescription. Patients were classified as remaining persistent with the index agent if they did not discontinue therapy prior to the month in question (% remaining on therapy = 100% − % discontinuing therapy). Time to therapy discontinuation was calculated as the number of days from the index prescription fill date to the date of index agent supply exhaustion preceding the gap of >60 days.

### Chronic Disease Burden

Patient chronic disease burden was assessed using a modified Chronic Disease Score (CDS) based on the method by Clark et al. The CDS utilized the presence of drug markers during the study period to identify the existence of chronic disease states (e.g., coronary/peripheral vascular disease, cardiac disease/congestive heart failure, hyperlipidemia, asthma, and diabetes mellitus). Individual disease states were weighted and summed to derive an overall score for each patient that represented the patient’s total chronic disease burden. Patient chronic disease burden was classified as mild, moderate, or severe based on score thresholds set using clinical criteria: mild = CDS of 0 to 3; moderate = CDS of 4 to 11; and severe = CDS >11.

In addition to the CDS, the use of other drugs for managing cardiovascular disease was evaluated for the entire cohort. Drug classes of interest included beta-blockers, digitalis, nitrates, antihyperlipidemic agents, diuretics, combination diuretic for-
mulations (e.g., with ACEI or beta-blocker), and antiplatelet agents. Patients were classified as “yes” or “no” based on whether they received medications from any of these classes, in addition to the index agent, during the study period.

### Statistical Analysis
All statistical and descriptive analyses were performed using SAS version 8.0 (Cary, North Carolina). Results for continuous variables are presented as means ± standard deviation. Analyses of variance (ANOVA) and covariance (ANCOVA) and t-tests were used for analyzing continuous data, while the chi-square test was used for categorical data. Multiple variable linear regression techniques were used to evaluate the impact of independent variables, such as age, gender, and CDS on compliance and MPR, and least square means were used to adjust outcome variables for effects of independent variables. A Cox proportional hazards regression model was used to evaluate risk of therapy discontinuation.

### Results
The new-start antihypertensive medication cohort consisted of 142,945 patients, 53% of whom were female, with a mean age of 63.1 years (Table 1). During the 2-year study period ended July 31, 2000, more than one half (51%) of the cohort initiated therapy on amlodipine, while 28% received lisinopril and 21% received valsartan. The mean CDS for the entire cohort was 10.15 ± 6.00 and essentially was comparable for all groups (Table 1). Valsartan patients had a slightly lower CDS (mean, 9.62 ± 5.66, P <0.0001) compared with lisinopril (mean, 10.19 ± 5.96) or amlodipine (mean, 10.34 ± 6.15) patients, and a significantly smaller proportion of valsartan patients was classified as having a severe chronic disease burden (31% versus 35% for lisinopril and amlodipine, P <0.0001). The most common concomitant cardiovascular medications used during the study period included diuretics in 34.7% of patients, antihyperlipidemic therapy in 31.8%, and beta-blockers in 25.5% (Table 2). Valsartan patients were less likely to be prescribed concomitant cardiovascular medications.

Overall, 54% of the study cohort remained on therapy with their index agent at 12 months following the initial prescription. A significant difference was observed in therapy persistence among the study agents: 63% of valsartan patients compared with 53% of amlodipine patients (P<0.001) and 50% of
lisinopril patients (P<0.001) remained on therapy at 12 months (Figure 2). Mean time to therapy discontinuation also was significantly longer for valsartan patients: 270.1 ± 131.2 days versus 241.6 ± 140.2 days (P<0.001) and 234.6 ± 141.1 days (P<0.0001) for amlodipine and lisinopril patients, respectively (Table 3). Patients using valsartan had significantly higher compliance (mean compliance = 88.5% for valsartan versus 86.7% for amlodipine and 86.3% for lisinopril, P<0.0001 for both) and MPR (mean MPR = 75.6% for valsartan versus 67.5% for amlodipine and 64.8% for lisinopril, P<0.0001 for both) (Table 3).

A multiple linear regression model, controlling for study independent variables, found that treatment group, age, gender, CDS, and use of antihyperlipidemic agents (yes/no), beta-blockers (yes/no), and nitrates (yes/no) were all significant predictors of compliance. Use of diuretics and combination diuretic products, antiplatelet agents, and digitalis significantly predicted patient MPR. However, when compliance and MPR were adjusted for significant covariates, valsartan patients remained significantly more compliant; the adjusted mean compliance for valsartan was 88.9% compared with 86.6% (P<0.0001) for amlodipine and lisinopril, while the adjusted MPR for valsartan was 75.3% compared with 67.2% (P<0.0001) for amlodipine and 64.6% (P<0.0001) for lisinopril.

A Cox proportional hazards model, with valsartan as the reference agent, was used to assess therapy discontinuation while controlling for gender, age, CDS, and use of other agents for hypertension. Patients who initiated therapy on lisinopril (hazards ratio, 1.45; P<0.0001) or amlodipine (hazards ratio, 1.33; P<0.0001) were more likely to discontinue therapy within the first 12 months than were valsartan patients (Table 4).

This study has demonstrated that therapy with valsartan was associated with better patient compliance and persistence compared with either lisinopril or amlodipine in a usual-care setting. Improved compliance and persistence with valsartan may be related to better tolerability, as suggested by a lower discontinuation rate during the first year of therapy. In a survey of 2,115 patients and 336 physicians in the United Kingdom, Lip et al. demonstrated that 34% of patients reported unacceptable side effects with hypertension therapy, and physicians reported that 42% of medication switches were due to side effects.21 The data from this study are also consistent with findings from other utilization studies,7,22,26 which demonstrated that the choice of antihypertensive agent has an important impact on persistence rates with a therapeutic regimen. In addition, this research corroborates other studies that have found ARBs to be associated with improved patient compliance and lower discontinuation rates compared to other antihypertensive drug classes including ACEIs and CCBs.7,22,27

Persistence with antihypertensive medications has proven effective for decreasing the long-term consequences of untreated hypertension,28 as well as reducing the consumption of health care resources during the first year of therapy.29 The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) recommends thiazide diuretics as initial therapy for hypertensive patients without comorbidities.30 However, the benefit of diuretics on morbidity and mortality, as demonstrated by randomized clinical trials, may not be fully realized in the usual-care setting, where compliance and persistence with therapy may not be optimal.

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), patients using the thiazide diuretic chlorthalidone had similar mortality results as patients prescribed amlodipine or lisinopril and experienced less cardiovascular morbidity.31 In the ALLHAT study, a randomized trial but without the continuous follow-up of a typical randomized clinical trial, 87% of chlorthalidone patients were persistent at 1 year and 81% at 5 years posttherapy initiation. In contrast, other observational studies have shown much lower persistence rates with thiazide diuretics in nonclinical trial settings21,22,27; one study found that at 1 year, only 21% of patients remained on medication, and at 4 years, only 16% were persistent with thiazide diuretics.27 Interestingly, valsartan patients in the present study less frequently used other cardiovascular medications as compared to lisinopril or amlodipine patients. These results suggest that these medications are being used as initial therapy in many patients, in contrast to JNC 6 and JNC 7 guidelines.

**Limitations**

Since this analysis used administrative pharmacy claims, it is important to recognize some study limitations. First, the analy-
drug regimens. Adjusting outcome metrics for CDS, which may have more motivation to be compliant with prescribed hypertension. Patients experiencing disease symptoms heart failure or angina, which are more symptomatic diseases. These drugs may have been used in patients with congestive indications other than hypertension as the primary indication. Selection of these drugs by the prescriber may have included severity was not available from pharmacy claims data, so the cations for use. Information on patient diagnosis and disease hypertension, but many of the medications have multiple indi-

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Crude and Adjusted MPR and Compliance Results</th>
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<tr>
<td>Characteristic</td>
<td>Amlodipine (n=73,148)</td>
</tr>
<tr>
<td>Mean days to therapy discontinuation (±SD)</td>
<td>241.6 ± 140.2</td>
</tr>
<tr>
<td>Crude (unadjusted) mean compliance (±SD)</td>
<td>86.7 ± 20.2</td>
</tr>
<tr>
<td>Crude (unadjusted) mean MPR (±SD)</td>
<td>67.5 ± 37.6</td>
</tr>
<tr>
<td>Adjusted† mean compliance (±SE)</td>
<td>86.6 ± 0.001</td>
</tr>
<tr>
<td>Adjusted mean† MPR (±SE)</td>
<td>67.2 ± 0.14</td>
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</tbody>
</table>

* P value calculated using analysis of variance for comparisons of crude means and least squares regression for adjusted means. † Adjusted for age, gender, and CDS using least square regression.

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Results of Cox Proportional Hazards Model for Therapy Discontinuation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Cox Proportional Hazards Ratio</td>
</tr>
<tr>
<td>Age</td>
<td>0.993</td>
</tr>
<tr>
<td>Male</td>
<td>0.954</td>
</tr>
<tr>
<td>CDS</td>
<td>1.013</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>1.333</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.446</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1.103</td>
</tr>
<tr>
<td>Diuretic combination†</td>
<td>1.544</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>1.131</td>
</tr>
<tr>
<td>Nitrates</td>
<td>1.137</td>
</tr>
<tr>
<td>Antihyperlipidemic agents</td>
<td>0.743</td>
</tr>
<tr>
<td>Digitalis</td>
<td>1.049</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>1.032</td>
</tr>
</tbody>
</table>

* Reference agent=valsartan. † Includes diuretic combined with angiotensin-converting enzyme inhibitor, calcium channel blocker, or beta-blocker. CDS = Chronic Disease Score.

s used drug markers to proxy the presence of cardiac disease, should address this limitation; however, using drug markers to identify disease states may not be as accurate as medical record review or prospective data collection.

This study also did not include measures of clinical effectiveness (blood pressure control) or outcomes (morbidity and mortality) for the evaluated cohort of patients. Many of the patients in the current study were using other antihypertensive medications and had other comorbidities according to the CDS; therefore, the results of the current study may not apply solely to patients with simple hypertension. Finally, as in all studies of drug claims data, the study population included only persons with pharmacy benefits coverage, and these study results may not reflect the drug-taking behavior of patients without some form of insurance for prescription medications.

**Conclusion**

This observational study demonstrated that patients in a usual-care setting who receive valsartan therapy, compared to the CCB amlodipine and the ACEI lisinopril, have greater persistence and compliance. These findings suggest that agent selection for chronic pharmacologic management of hypertension has the potential to affect patient drug-taking behavior and perhaps longer-term outcomes in a typical real-world setting.

**DISCLOSURES**

Funding for this research was provided by Novartis Pharmaceuticals Corporation, Inc., via a grant to The Institute for Effectiveness Research, a subsidiary of Medco Health Solutions, Inc., and was obtained by author Jenifer Wogen. Wogen and authors Charles A. Kreilick and Richard C. Livornese are employed by The Institute for Effectiveness Research, author Feride Frech is employed by Novartis. Wogen served as principal author of the study. Study concept and design were contributed primarily by Wogen and Frech. Analysis and interpretation of data were contributed by Wogen, Kreilick, and Livornese. Drafting of the manuscript and its critical revision were the work of Wogen, Frech, and author Krista Yokoyama. Statistical expertise was contributed by Wogen and Kreilick, and administrative, techni-

**REFERENCES**


