

After the Diagnosis: Adherence and Persistence With Hypertension Therapy

Abstract

Poor adherence to therapy is a major reason that a large percentage of patients with hypertension fail to achieve good blood pressure control. Side effects, such as cough, dizziness, nausea, and headache, are frequently cited as reasons for lack of adherence and persistence with hypertension therapy. Use of newer classes of antihypertensive agents with better tolerability than older agents may be one way to improve adherence and persistence. Recent studies have shown higher rates of adherence and persistence with therapy in patients treated with angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, or newer calcium channel blockers compared with other antihypertensive agents. Health insurance coverage can also affect patient adherence and persistence.

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High blood pressure (BP) significantly increases overall cardiovascular (CV) risk.¹ The incidence of stroke increases approximately 3-fold in patients with borderline hypertension and approximately 8-fold in those with definite hypertension.²⁻⁴ An estimated 40% of cases of acute myocardial infarction or stroke are attributable to hypertension.^{3,4} Yet, despite the established burden of this condition and the availability of effective treatments, studies have shown that only about 30% of Americans with hypertension have their BP controlled.⁵

It is believed that poor adherence to therapy contributes to lack of good BP control in more than two thirds of people living with hypertension.⁶ As many as half of all patients who use antihypertensive drugs have been found to discontinue treatment within follow-up periods ranging from 6 months to 4 years.⁷⁻¹⁰ Given the economic burden of untreated hypertension—the cost of healthcare related to hypertension and

its complications is nearly \$60 billion annually¹¹—improving adherence has far-reaching health and economic ramifications for individuals, healthcare delivery systems, and our nation as a whole.

Adverse Effects and Patient Adherence

Although multiple factors contribute to patient adherence to medications,¹² a common problem with hypertension treatment in particular is that agents that decrease BP can cause adverse events in patients who may not have experienced any symptoms attributable to this CV condition. Side effects like dry cough, dizziness, nausea, and headache associated with some treatments¹³ may interfere with adherence, because patients weigh these immediate problems against the long-term benefits of treatment.¹⁴ Nonadherence with antihypertensive therapy is commonly attributed to these tolerability issues. A study of 948 patients in the United Kingdom found that 42% of all changes in antihypertensive therapy were due to side effects.¹⁵ In a survey of 623 patients, 41% of all patients reported adverse effects, and nearly half of these patients independently modified their regimen.¹⁶ Those reporting problems with their medications were 3.5 times more likely to reduce their doses or discontinue therapy than patients not reporting problems.

Strategies for Improving Adherence

Several alternatives can be considered to improve adherence and persistence. Convenient dosing schedules contribute to adherence to treatment not only for hypertension, but across a wide range of therapeutic areas.¹⁷ Even so, a 20-year review of the literature found only a 76% adherence rate for once-daily hypertensive medication.¹⁸

Newer antihypertensive drug classes with

better tolerability may provide another option for improving patient persistence with prescribed therapy. In a retrospective cohort study by Bloom, the prescription records of a pharmaceutical benefits management organization were used to analyze the refill behavior of outpatients who had recently begun antihypertensive therapy.¹⁰ In this large patient population (N = 21 723), angiotensin receptor blockers (ARBs) had the highest rate of persistence (64%), followed by angiotensin-converting enzyme inhibitors (ACEIs, 58%), calcium channel blockers (CCBs, 50%), beta blockers (43%), and thiazide diuretics (38%).

A longitudinal analysis of a subset of this study cohort (N = 15 175) identified from the same pharmacy administrative claims database reported 4-year persistence patterns associated with the major drug classes used in hypertension.¹⁹ Consistent with earlier findings reported by Bloom,¹⁰ the study by Conlin and associates¹⁹ showed that the number of patients staying on therapy from 12 to 48 months was significantly greater among patients using an ARB than among those using other antihypertensive drug

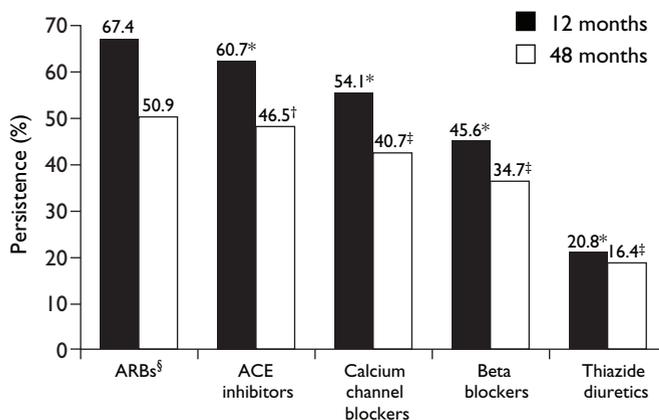
classes (Figure 1). At 48 months, however, persistence with ARB therapy, although still significantly greater than persistence with CCBs, beta blockers, and thiazide diuretics, was not significantly higher than persistence with ACEIs.

A recent clinical practice-based analysis conducted in Italy examined the records of 14 062 new users of antihypertensive drugs who were followed for 12 months.²⁰ The authors evaluated the relationship between drug class and persistence. Patients who were given an ARB as initial therapy showed a greater tendency to stay on antihypertensive therapy compared with those who initiated therapy with ACEIs, CCBs, or diuretics. The risk of discontinuing treatment for those classes was 38.6%, 66.3%, and 85.3% greater, respectively, than among patients using ARBs. Nonpersistence with treatment was also associated with increased age, concurrent long-term pharmacologic treatments, and previous hospital admission for CV disease.

Costs associated with persistent drug use versus nonadherence were also reported. The annual cost for antihypertensive drug therapy was related to patient age, pattern of persistence, number of drug classes prescribed, and class of antihypertensive drug prescribed at enrollment. Multiple regression analysis showed that the specific drug prescribed at enrollment and the pattern of persistence were the variables that best correlated with the cost of drug therapy (Table). Annual costs for patients who combined or switched drug classes were higher than for patients who stayed on the medication initially prescribed.

New data presented at the 2005 American Society of Hypertension (ASH) scientific meeting support these earlier reports. A 2-year, retrospective, longitudinal pharmacy claims database analysis evaluated claims from approximately 11 million individuals with pharmacy benefit coverage who were initiating antihypertension therapy.²¹ Two different measures were used: persistence, defined as the percent of patients who remained on therapy with the index agent, and adherence, defined as the total days supply of all index medication (excluding last fill) divided by duration of therapy.

Figure 1. Four-year Persistence Patterns Among Patients Initiating Therapy With the Angiotensin Receptor Blocker Versus Other Antihypertensive Drug Classes



*P < .01 versus ARBs.

[†]P = .095 versus ARBs.

[‡]P < .03 versus ARBs.

[§]At 48 months, 92% of the ARB cohort was taking losartan versus other ARBs. ARBs indicates angiotensin receptor blockers; ACE, angiotensin-converting enzyme.

Source: Reference 19.

Table. Multiple Linear Regression Analysis of Cost of Drug Treatment

| Factor | Reference category | Regression coefficient (B) | 95% CI | P value |
|-----------------------------------|---|----------------------------|---------------|---------|
| Age | | -0.43* | -0.81- -0.05 | .027 |
| Compliance pattern | Increased cost compared with patients who stayed on initial therapy | | | |
| Combining the class at enrollment | | 26.35 | 11.37-41.34 | .001 |
| Switching the class at enrollment | | 33.17 | 18.65-47.70 | <.001 |
| Number of different classes | | 10.94† | 2.62-19.27 | .010 |
| Class at enrollment | Increased cost compared with diuretics | | | |
| Beta blockers | | 67.45 | 49.71-85.20 | <.001 |
| CCBs | | 188.84 | 172.81-204.87 | <.001 |
| ACEIs | | 168.20 | 153.05-183.35 | <.001 |
| ARBs | | 278.19 | 258.84-297.54 | <.001 |

*Related to 1-year age increment.

†Related to 1 unit increment.

CI indicates confidence interval; CCBs, calcium channel blockers; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Source: Reference 9.

Persistence results showed that after adjusting for age and sex, the risk of discontinuation was 39%, 62%, and 24% higher for amlodipine, hydrochlorothiazide (HCTZ), and lisinopril, respectively, compared with the ARB valsartan ($P < .01$). More valsartan-treated patients (40%) remained persistent at 24 months compared with those receiving HCTZ (25%), amlodipine (30%), or lisinopril (35%) ($P < .01$). Results also showed that adherence was greatest for valsartan-treated patients (77%) compared with 72% for amlodipine, 70% for HCTZ, and 73% for lisinopril ($P < .05$) (Figure 2a, 2b).²¹

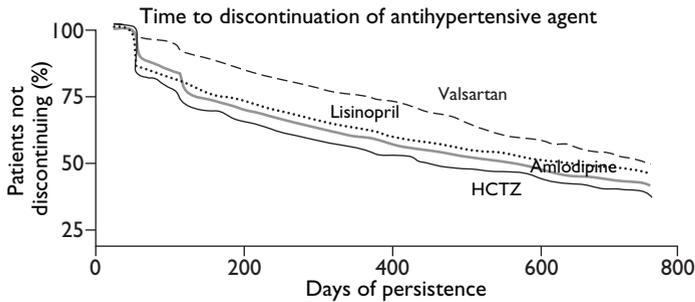
A smaller study of 347 patients also presented at ASH reported favorable adherence for ARB therapy, but also found that patients treated with the CCB lercanidipine or ACEIs achieved comparable adherence at 6 months, with only 7% changing therapies.²² However, a high proportion of individuals treated with thiazide diuretics, beta blockers, and other CCBs modified their therapy. At 24 months, ARBs had the highest adherence rate (78.5%), followed by ACEIs and lercanidipine (74.5% and 67.3%, respectively [$P < .05$]).

Interventions used to increase medication adherence include educational interventions, patient behavioral interventions, and provider interventions.²³ With a few exceptions, systematic reviews have shown that interventions involving patient educational methods have been ineffective when used alone. More positive results have been reported for behavioral interventions, which appear to not only improve medication adherence but also clinical outcomes.²⁴ Provider education interventions are reported to achieve substantial increases in patient adherence.²⁴⁻²⁶

Insurance Status and Adherence

Costs of drugs to the patient and insurance status can also affect treatment adherence and persistence. Huskamp and associates assessed the effect of incentive-based formularies, which provide financial incentives for enrollees to choose drugs preferred by the payer, on prescription drug utilization and spending.²⁷ Using claims data, the investigators studied the use of prescription drugs (statins, ACEIs, and proton pump

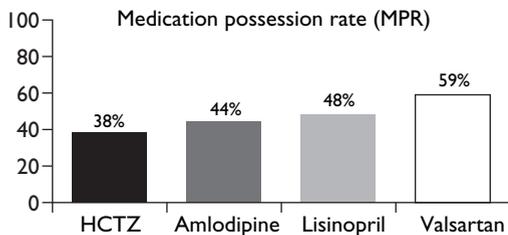
Figure 2a. Persistence



- Adjusting for age and sex, risk of discontinuation was 39%, 62%, and 24% higher for amlodipine, HCTZ, and lisinopril, respectively, compared with valsartan ($P < .01$).
- More patients taking valsartan (40%) remained persistent at 24 months past the index date of the first prescription compared with HCTZ (25%), amlodipine (30%), and lisinopril (35%) ($P < .01$).

HCTZ indicates hydrochlorothiazide.

Figure 2b. Adherence



- $P < .05$ (valsartan vs others).
- Compliance was greatest for patients taking valsartan (77%) compared with 72% for amlodipine, 70% for HCTZ, and 73% for lisinopril ($P < .05$ for all comparisons to valsartan).
- MPR was greatest for patients taking valsartan compared with HCTZ, amlodipine, and lisinopril ($P < .05$ for all comparisons to valsartan) after 2 years.

HCTZ indicates hydrochlorothiazide.

Source: Reference 21.

inhibitors) by employees and their dependents who had healthcare coverage from 2 large employers. Both employers had recently made changes in their pharmaceutical benefits. Employer 1 switched from a 1-tier to a 3-tier formulary and increased copayments for all prescription drugs. Employer 2 made a less dramatic change from a 2-tier to a 3-tier formulary. An intervention group and a comparison group of enrollees were identified for each employer.

The benefits change made by Employer 1 had marked effects on use of drugs and enrollees' out-of-pocket expenditures. Many enrollees in the intervention group switched

to a drug of a lower tier (with lower copayments), and some stopped taking medications entirely in these classes. In contrast, the more moderate changes made by Employer 2 had modest effects on drug use and expenditures by enrollees.

Conclusion

Research presented at the 2005 ASH scientific meeting supports earlier reports that adherence is greater among ARB-treated patients than in those receiving other antihypertensive agents. One study, however, showed that patients using ACEIs and the CCB lercanidipine were also highly adherent. Collectively, these findings suggest that drug selection may have an impact on persistence and adherence to antihypertensive therapy.

Nonadherence and interruption of antihypertensive drug treatment have important economic implications, because patients who fail to adhere to medication regimens cannot realize the protective CV benefits that are associated with sustained treatment. In the selection of pharmacotherapy for hypertension, consideration should be given to use of medications that may be more or less likely to facilitate good long-term control. If control of hypertension is more likely when adherence is high, drugs with which patients are likely to adhere should be used preferentially.

Ultimately, consistent control of BP rests in the hands of the patient, who must follow medication and dietary regimens. Providers can contribute to this effort by simplifying instructions to the patient and medication schedules, so that the total number of daily doses are minimized.²⁸ Certainly both patients and physicians would agree that medications seldom work when left in the bottle.

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