Review Paper

Improving Outcomes in Hypertensive Patients: Focus on Adherence and Persistence With Antihypertensive Therapy

William J. Elliott, MD, PhD

Although effective control of blood pressure (BP) reduces the risk of cardiovascular events in patients with hypertension, BP control rates among treated patients in actual clinical practice are less than optimal. Although the costs of medicines and medical care (which are difficult to estimate both in clinical trials and general clinical practice) are important, medication-taking behavior—adherence and persistence with antihypertensive regimens—influences BP control rates. Many factors affect adherence and persistence with medications, including efficacy and tolerability of drugs prescribed, such that rates vary greatly among antihypertensive classes. In general, medications with fewer adverse effects (in registration trials or large outcomes studies) are associated with increased adherence and lower discontinuation rates. More widespread use of such agents, particularly those available in generic formulations or in low-cost formularies, may lead to better long-term BP control and fewer cardiovascular events. J Clin Hypertens (Greenwich). *2009;11:376–382.*

From the Department of Preventive Medicine, Rush Medical College at Rush University Medical Center, Chicago, IL
Address for correspondence: William J. Elliott, MD, PhD, Department of Preventive Medicine, Rush Medical College, 1700 West Van Buren Street, Suite 470, Chicago, IL 60612
E-mail: wj.elliott@yahoo.com
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Extensive evidence has demonstrated that effective control of blood pressure (BP) reduces the risk of cardiovascular events in patients with hypertension.[1,2] Data from placebo-controlled clinical trials indicate that reductions of 10 mm Hg to 12 mm Hg in systolic BP or 5 mm Hg to 6 mm Hg in diastolic BP, or both, lower the risk of stroke by 38%, cardiovascular death by 21%, and coronary heart disease by 16%.[3] BP control rates in recent major clinical trials have ranged from 66% in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[4] to almost 80% in the US arm of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial.[5] However, despite the importance of achieving BP control, hypertension control rates (<140/90 mm Hg, at minimum) remain suboptimal in actual clinical practice. According to the most recent results of the National Health and Nutrition Examination Survey (NHANES) 2005–2006, the estimated BP control rate among all hypertensive patients is 44% and among treated hypertensive patients is 64%.[6] These rates are similar to those reported recently by the National Ambulatory Medical Care Survey of physicians in office settings: only 39% to 44% of treated hypertensive patients were at recommended BP levels.[7,8] These

numbers fall short of the Healthy People 2010 target of BP control in 50% of all hypertensive patients,[9] and leave room for considerable improvement.

The discrepancy between clinical trial results of good BP control and actual clinical practice is due to a number of factors, including differences in medication-taking behavior, ie, adherence and persistence with drug therapy regimens. Adherence is defined as the appropriate use of therapy, including taking medications at the prescribed frequency/interval and dose/dosing regimen.[10,11] Adherence is reported as the percentage of prescribed doses taken per defined period of time and is a dynamic parameter that can change over time, as when a patient becomes more adherent with therapy just before a visit to the physician. The leading problem associated with adherence is lack of persistence with drug therapy.[12] Persistence on the other hand is defined as continuing the use of a medication(s) for the specified treatment period and is measured in terms of time (eg, days, weeks, months).[10,11] Historically, however, compliance was used as a catchall term that encompassed a patient's adherence and persistence.

In the past 5 years there has been a shift away from use of the term compliance to adherence to describe the correspondence of a patient's medication-taking behavior with prescriber recommendations.[10,13,14] The rationale for this change in terminology is that compliance implies professional dominance in the social contract between the health care provider and patient, whereas adherence suggests that a patient can be a partner in medical decision-making.[13,14] In hypertension, adherence is less likely to be confused with "arterial compliance," an important topic in its own right. In the United States, the term compliance has been largely appropriated by quality-assurance experts, and refers to the correspondence of treatment patterns and behaviors of health care professionals with recommended national guidelines. Nonetheless, both terms continue to be used in the medical literature.[11,14]

FACTORS RELATED TO POOR ADHERENCE AND PERSISTENCE

Factors contributing to the lack of adherence and persistence with therapy have been grouped into 5 categories: patient-related, condition-related, therapy-related, health system–related, and socioeconomic factors (Table I).[15] Patients may have a poor understanding or may lack awareness of the long-term consequences of elevated BP or the importance of BP control, particularly because hypertension is often asymptomatic and life-long (condition-related).[14] Lack of awareness may be particularly relevant for newly diagnosed hypertensive patients, who generally have lower persistence rates than patients with established hypertension.[16–18]

Table I. Categories of Factors Contributing to Lack of Adherence and/or Persistence With Antihypertensive Medication

Category	Factors Related to Hypertension
Patient-related	Lack of understanding of importance of achieving BP control, lack of understanding regarding how to take medications, perceived lack of drug efficacy, quality of life
Physician-related	Failure to modify therapy to meet BP goals, failure to involve patient in decision-making, insufficient patient education
Condition-related	Asymptomatic, life-long
Therapy-related	Adverse effects, complexity of regimen, cost
Health system–related	Access to health care, lack of follow-up, convenience of appointment scheduling
Socioeconomic	Differential treatment of socioeconomic and ethnic groups, lack of insurance, lack of transportation, lack of social support system

Abbreviation: BP, blood pressure. Adapted from the World Health Organization 2003.[15]

Other factors contributing to poor adherence and persistence are therapy-related. Complex medication regimens—multiple drugs and/or multiple doses per day—have been shown to decrease adherence,[19] as has a high total number of medications.[20] Initial choice of therapy, either a monotherapy or a combination regimen, can affect adherence and persistence as well.[21]

The contributions of adherence and persistence to the total cost of care are complex. The influence of economic factors on adherence and persistence are difficult to estimate, both for clinical trials and in general medical practice. Patients in research protocols often receive study medications free of charge and some of their medical care costs are reduced, compared with care outside of the research setting. Most recent estimates of persistence and adherence are derived from pharmacy

records, which do not capture prescriptions that are not filled. Studies of pharmacy databases seldom account for potential economic confounders, such as differences across drug classes in pharmacy copayments, tiered formularies, or nongeneric formulations. Across many studies, lack of health insurance, particularly among treated patients, correlates with poor adherence,[22] as does the level of drug copayment among the insured.[23–25] Cost-related nonadherence is more likely among patients with mood disorders and those with a heavy disease burden, regardless of drug coverage status, poverty status, or out-of-pocket drug costs.[26] However, health system–related factors may also apply, as many groups with health insurance and access to medical care, such as Medicare beneficiaries and US military veterans, sometimes have suboptimal BP control, although recent data from the veteran population suggest that changes in the health care system can improve BP control.[27,28]

WHO IS ADHERENT?

The NHANES database provides some indication of factors often associated with discontinuing antihypertensive drug therapy.[29] Nonpersistence with antihypertensive drug therapy was 12 times higher in younger (<30 years) than in older patients (>50 years), 31% higher in men than in women, and 43% higher in Hispanic patients compared with other racial/ethnic groups. Other factors include having a low income, having no health insurance, and not having visited a physician within the previous year.[29] Other investigators have identified greater adherence and persistence in hypertensive patients with concomitant cardiovascular conditions.[30]

CONSEQUENCES OF POOR ADHERENCE AND PERSISTENCE

The consequences of poor adherence and persistence with antihypertensive drug therapy are the same as those for hypertension itself—a higher risk for cardiovascular disease, hospitalization, and increased health care utilization and cost.[10,31] A study that evaluated adherence to angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and/or β-blockers in patients with ischemic heart disease and diabetes mellitus found that patients who were adherent were at lower risk for all-cause mortality (odds ratio, 0.52; 95% confidence interval, 0.39–0.69), and that nonadherent patients had a mortality risk that was similar to those who had not been prescribed these agents.[32] The impact of persistence on the primary prevention of myocardial infarction and stroke was also analyzed: nonpersistence with antihypertensive drug therapy was associated with a 15% increase in the risk of acute myocardial and a 28% increase in the risk of stroke in patients who were evaluated for an initial 2-year period followed by an additional 2-year period or until a cardiovascular event occurred.[33] Likewise, a retrospective cohort study of hypertensive men and women aged 65 years or younger found that the 1-year risk of hospitalization was significantly lower for patients who were 80% to 100% adherent with their antihypertensive regimen than those who were not.[34] Although drug costs were higher, overall medical costs were lower for patients who were 80% to 100% adherent compared with those with other adherence levels and were significantly better than those with adherence levels ≤59%.

Independent of adherence, higher BP is also associated with increased health care utilization and number/frequency of physician visits. In an analysis of 1000 hypertensive patients in managed care, higher maximum BP was significantly correlated with increased drug costs and number and frequency of physician visits.[35] Drug costs were approximately 1.8 times higher and the number of visits 1.8 to 2.4 times higher in patients with BP ≥160/100 mg Hg than in those with BP <130/85 mm Hg. The mean interval between physician visits was also shorter in patients with uncontrolled BP.[35]

ADHERENCE AND PERSISTENCE WITH ANTIHYPERTENSIVE REGIMENS

Typically, about 50% of patients discontinue antihypertensive therapy after 1 year,[10] a rate comparable with that of other long-term therapies for relatively asymptomatic conditions.[36] Reports of long-term persistence with antihypertensive therapy range from 14%[37] to 73%[18] at 1 year; from 9%[38] to 59%[18] at 3 years, from 16% to 51% at 4 years,[39] and up to 39% at 10 years.[40] In one study, the median time to overall discontinuation of antihypertensive drug therapy was 3.07 years.[41] Numerous studies of antihypertensive agents published over nearly a decade have consistently demonstrated higher persistence rates with some classes than with others. Generally, inhibitors of the renin-angiotensin system (RAS) have the highest persistence rates and diuretics the lowest rates (Table II).[17,18,21,37–39,41–45]

Adherence rates by antihypertensive drug class generally parallel those for persistence rates. In one analysis, after controlling for age, sex, year of initial prescription, and Charlson Comorbidity Index, adherence rates were 90.1% for valsartan, 89.9%

Table II. Persistence With Antihypertensive Medication Over Time by Drug Class

Study	No.	Persistence Rate (%) Diuretic	β-Blocker	CCB	ACEI	ARB
1 Year						
Bloom 1998[42]	21,723	38	43	50	58	64
Conlin 2001[39]	15,175	21	46	54	61	67
Hasford 2002[21]	2,416	34	50	44	42	51
Bourgault 2005[17]	21,326	45	50	55	59	66
Erkens 2005[43]	2,243	33	35	35	60	62
Perreault 2005[18]	14,947	61	68	68	71	73
Hoer 2007[37]	62,745	26	14	34	34	53
Patel 2007[44]	242,882	30	40	38	48	52
Elliott 2007[45]	60,685	56	–	60	65	69
3 Years						
Bourgault 2005[17]	21,326	29	34	38	40	53
Hasford 2007[38]	13,763	9	13	12	14	11
Perreault 2005[17]	21,011	48	57	58	58	59
4 Years						
Burke 2006[41]	109,454	31	33	35	40	42
Conlin 2001[39]	15,175	16	35	41	46	51

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

for lisinopril, 85.2% for amlodipine, and 78.6% for hydrochlorothiazide.[45] These findings are in agreement with earlier reported 1-year adherence rates for an ARB (88.9%), an ACE inhibitor (86.6%), and a dihydropyridine calcium channel blocker (CCB).[46]

Discontinuation rates are a different measure of medication-taking behavior that is related to persistence. In a recent study, discontinuation rates for various antihypertensive drug classes during the first year were 44.2% with a diuretic, 39.7% with a CCB, 35.2% with an ACE inhibitor, and 30.6% with an ARB.[45] The time to discontinuation of therapy was 137.0 days overall and ranged from 116.2 days for a diuretic to 177.5 days for ARB therapy, a significant difference.[45] Preliminary reports of meta-analyses (including 18 studies involving 631,579 patients) found the same rank order for discontinuation of original antihypertensive drug after 1 year (from most to least likely) as follows: diuretic >β-blocker >CCB >ACE inhibitor >ARB.[47,48] The differences were significant for all classes compared with the diuretic. This larger and more comprehensive analysis confirms and extends the findings from earlier studies.[17,18,39,41,42]

A variety of factors influence persistence with antihypertensive medication (Table III),[17,18,39,40,42,45,49–52] but one of the most significant may be adverse effects. This is particularly relevant since hypertension is often asymptomatic. In a prospective cohort study of patients starting a new antihypertensive agent, discontinuation rates of 12% at 1 month and 24% at 3 months were largely attributable to the incidence of adverse effects, as patients reporting adverse effects were almost twice as likely to discontinue treatment as those who did not.[52] A 2001 meta-analysis of discontinuations specifically due to adverse events according to antihypertensive drug classes found that CCBs, β-blockers, and ACE inhibitors had higher discontinuation rates than placebo, while diuretics and ARBs had lower discontinuation rates.[53] In actively controlled trials,

Table III. Factors Influencing Persistence With Antihypertensive Medication Regimens and Discontinuation of Therapy

Factor	Finding
Age	Older patients more persistent than younger patients
Sex	Women usually more persistent than men
Initial monotherapy	Persistence highest with angiotensin receptor blockers, lowest with diuretics
Comorbidity	Discontinuation rates higher with higher comorbidity index
Adverse effects	Occurrence of adverse effects increases discontinuation
Prescription coverage	Discontinuation rates lower with drug coverage

higher discontinuations due to adverse effects were noted for diuretics and β-blockers vs CCBs and for ARBs vs ACE inhibitors.

COMBINATION REGIMENS

More than two thirds of patients require ≥2 antihypertensive agents (typically having complementary mechanisms of action) to achieve their BP goal. Moreover, patients with diabetes mellitus, chronic kidney disease, or heart disease now have a lower BP target (<130/80 mm Hg) and may require ≥3 agents.[1,54] Fixed-dose combination pills provide improved BP lowering, often with a lower frequency and/or severity of side effects, compared with higher doses of the individual agents, which may improve tolerability. Pills containing appropriately chosen agents can reduce pill burden and increase long-term adherence. Persistence rates for combination therapy at 1 year are significantly better than rates for monotherapy with diuretics, β-blockers, and/or CCBs.[18,46]

A low dose of a thiazide-type or thiazide-like diuretic enhances the efficacy of most other antihypertensive agents with no increase in the occurrence of adverse events.[55–58] The combination of an ACE inhibitor or ARB with a CCB also has significantly greater BP-lowering effects and a lower incidence and severity of peripheral edema, compared with high-dose CCB monotherapy,[55,59,60] which may result in improved tolerability and higher persistence. A recent meta-analysis of 42 factorial-design trials involving 10,968 patients given a thiazide diuretic, β-blocker, CCB, or ACE inhibitor showed approximately a 5-fold greater reduction in BP with the combination of 2 of these drug classes, compared with doubling the dose of one drug.[61] In contrast, some combinations can be troublesome. Although a combination of an ARB and an ACE inhibitor has been approved by the US Food and Drug Administration for patients with heart failure and to reduce proteinuria,[62] a greater risk of adverse effects,[63] and poorer outcomes in high-risk cardiovascular patients have been noted.[64]

STRATEGIES TO IMPROVE ADHERENCE AND PERSISTENCE

Since the many factors that contribute to poor adherence and/or persistence with antihypertensive therapy (Table III) are not mutually exclusive, interventions to improve adherence and persistence with therapy are multidisciplinary and comprehensive in nature and include cognitive, behavioral, and affective strategies tailored to a specific patient.[10,65] Physicians often individualize antihypertensive regimens, taking into account the degree of BP elevation, concomitant conditions (eg, diabetes, chronic kidney disease), absolute cardiovascular risk, and an assessment of the patient's past medication-taking behavior. Involving the patient in treatment decisions as well as ensuring that the patient understands the consequences of hypertension and the importance of its treatment, providing adequate follow-up, and modifying the regimen as necessary to achieve the target BP level may also be important.

CONCLUSIONS

Many factors affect adherence and persistence rates, including efficacy and tolerability of drugs prescribed. A better understanding of adherence and persistence with antihypertensive medication regimens, factors affecting each, and strategies to improve medication-taking behavior likely will improve BP control rates and lower the economic burden of hypertension and its consequent cardiovascular effects.

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