Epidemiology and Unmet Needs in Hypertension

John M. Flack, MD, MPH, FAHA

ABSTRACT

BACKGROUND: The persistent control of blood pressure (BP) to levels below current recommended levels is an important but often elusive goal for patients with hypertension.

OBJECTIVE: To provide an overview of unmet needs in contemporary hypertension treatment.

SUMMARY: The rationale for BP normalization is very persuasive. Incrementally higher BP levels predict higher rates of microvascular (e.g., retinopathy, stroke, nephropathy) and macrovascular disease (e.g., myocardial infarction), as well as organ (e.g., heart) failure. Accordingly, the pharmacologic reduction of BP levels with a broad range of mechanistically dissimilar agents reduces the risk of these BP-related complications. The primary prevention of BP-related complications has been closely linked to the magnitude of decreases in BP brought about pharmacologically, but some modest disease-specific differences have been noted between drug classes. However, pharmacologic blockade of the renin-angiotensin aldosterone system in high-risk patients (e.g., patients with diabetic nephropathy) reduces the risk of BP-related renal end points more than treatment strategies that do not include these agents, even when BP levels are lowered to similar degrees.

CONCLUSION: Despite the large number of antihypertensive agents available, the majority of patients with hypertension who are treated with drugs do not attain goal BP levels. Though the reasons for this are complex and relate to various factors for patients, providers, and systems of medical care delivery, new pharmacologic treatments hold the potential to augment the reduction of BP levels while minimizing class-specific side effects.

KEYWORDS: Blood pressure, Vascular disease, Hypertensive agents, Hypertension

J Manag Care Pharm. 2007;13(8)(suppl S-b):S2-S8

Copyright© 2007, Academy of Managed Care Pharmacy. All rights reserved.

Author

JOHN M. FLACK, MD, MPH, FAHA, is a specialist in clinical hypertension and is principal investigator, Center for Urban and African American Health, Wayne State University, Detroit, MI. He is also a professor, interim chair, and chief of the Division of Translational Research and Clinical Epidemiology, Department of Internal Medicine, Wayne State University School of Medicine, and specialist-in-chief for internal medicine, Detroit Medical Center.

AUTHOR CORRESPONDENCE: John M. Flack, MD, MPH, FAHA, Harper Professional Building, Wayne State University, 4160 John R, Suite 1002, Detroit, MI 48201. Tel: (313) 745-4525; Fax: (313) 993-0085; E-mail: jflack@med.wayne.edu

Approximately 72 million people in the United States have hypertension. The prevalence of hypertension is increasing in both men and women across the age span, but more rapidly in women. Indeed, the age-adjusted prevalence of hypertension is higher in women than in men, and is also higher in black people than in members of other racial groups. If elevated blood pressure (BP) was “only a number,” then the monumental attention it has received over the last several decades in the medical community would be unwarranted. Thus it is important to understand that incrementally higher levels of BP—especially systolic BP (SBP)—beginning at levels well within the normal range, cause or promote microvascular and macrovascular diseases, as well as target-organ injury or failure. The absolute risk for BP-related cardiovascular disease (CVD) events is much higher when elevated BP levels coexist with other CVD risk factors, such as diabetes and dyslipidemia. Pharmacologic lowering of BP with mechanistically dissimilar antihypertensive agents reduces the risk of, but does not entirely prevent, BP-related CVD events, such as stroke, heart failure, retinopathy, and nephropathy.

Pharmacologic reduction of BP levels in patients with hypertension does not reduce risk of CVD and renal events to an incidence similar to that of normotensive individuals. Certainly, some of the residual risk in drug-treated patients with hypertension is attributable to BP levels that remain significantly above those in normotensive individuals. However, the risk of CVD and renal events remains higher in treated patients with hypertension than in normotensive patients, even when they have the same BP level.

This is an intuitively logical observation. Once BP is persistently elevated, which is undoubtedly both a consequence and a cause of vascular/organ injury, it seems implausible that total reversal of the underlying vascular/organ pathology will occur without prolonged reduction of BP levels that are well below currently recommended treatment targets. Accordingly, it is possible to argue that currently recommended BP target levels are not truly normal in a physiologic sense because they have been largely derived from clinical trial data that, until recently, did not reflect an attempt in the study to reduce BP levels to normal or near-normal levels. The Treatment of Mild Hypertension Study (TOMHS), an often overlooked trial, reported fewer cardiovascular events in relatively low-risk patients with hypertension when SBP was lowered to ~125 mm Hg compared with ~131 mm Hg. Thus, the anticipated benefit of reducing BP levels could be even greater among high-risk patients with hypertension, such as those with diabetes mellitus, who attained a very low BP level (e.g., <120/70 mm Hg), assuming that the reduction of BP to
such a level was both feasible and harmless. Given the current armamentarium of antihypertensive agents, this very low level will undoubtedly require a carefully assembled multidrug treatment strategy that will almost assuredly include a diuretic.

The holy grail of antihypertensive treatment is to persistently reduce BP to below goal levels with drug regimens that maximize target-organ protection. Reducing cuff BP levels has typically served as a reliable proxy for the primary prevention of BP-related target-organ complications. Indeed, most of the risk reduction for BP-related complications, especially in nonhigh-risk hypertensive patients, can be statistically linked very closely, though not exclusively, to the magnitude of the reduction of the BP level with mechanistically dissimilar antihypertensive agents.

As White discusses in another article in this supplement, lowering BP throughout the entire 24-hour time interval is highly desirable. The most accurate way to determine that BP control truly occurs throughout the day and night is to use ambulatory BP monitoring. A less accurate way to assess 24-hour BP control is to determine BP levels just before morning dosing when the hypotensive effect of antihypertensive medication(s) is at its nadir.

In patients with hypertension who are at higher risk, such as those with diabetic nephropathy or at high cardiovascular risk, the superiority of suppressing the renin-angiotensin aldosterone system (RAAS) with angiotensin receptor blockers (ARBs) compared with other antihypertensive agents has been repeatedly demonstrated, most often in renoprotection and reduction of target-organ complications, especially in renoprotection and reduction of target-organ protection using RAAS blockade in high-risk patients, both normotensive and hypertensive, has been encouraging but not consistent. It should be noted, however, that the reduction in the BP level occurs as a consequence of favorably altering vascular hemodynamics, intravascular volume status, and cardiac function in response to drug-induced changes in basic organ and cellular metabolism and function. Accordingly, the close statistical link between the reduction of BP level and the reduction of the risk of CVD events does not mean that BP reduction, occurring as a consequence of unmeasured changes in cardiac, vascular, and kidney function, is the sole mediator of CVD and renal risk reduction.

There are clinical end point data showing that different antihypertensive drugs lead to significantly different CVD outcomes, possibly on the basis of differential effects on intravascular hemodynamics. However, the largest hypertension end point trial ever conducted, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, found no difference in the primary, and prespecified secondary pressure-related, clinical outcomes between 2 of the 3 treatment strategies (amlodipine vs. chlorthalidone). However, there was a greater incidence of the combined CVD secondary end point with lisinopril than with chlorthalidone. Nevertheless, in nonhigh-risk patients with hypertension, even when differences in the primary prevention of clinical outcomes between drug classes have been noted, differences in outcomes tend to be organ specific, and the majority of CVD-renal outcomes do not consistently favor 1 drug class. Interestingly, a recently published comparison of hypertension guidelines in the United States and Europe indicated that lower hypertension guideline treatment thresholds and more intensive antihypertensive treatment in the United States was associated with better hypertension control compared with that seen in western Europe.

**Adequacy of Recommendations for Control of BP Levels**

Current BP reduction targets for high-risk patients with hypertension—those with diabetes, vascular disease, previous CVD or coronary heart disease, and/or kidney disease—have received criticism for not being evidence-based. The likely reason for such criticism is that the benefits and safety of these targets have not been demonstrated explicitly in a randomized clinical trial in which a treatment arm goal was specified to be a BP of <130/80 mm Hg. However, though clinical trials provide a high level of evidence-based information, data from any trial must be both interpreted and considered in the context of all the available information, including previous clinical trials, rigorous observational studies, and physiologic and basic science observations.

If BP levels are to be persistently maintained below recommended goal levels, then practitioners must aim to drive BP levels well below these target BP levels. Thus, goal BP levels must be considered more like ceilings than floors. Even nonhigh-risk hypertensive patients will likely manifest residual risk for pressure-related CVD sequelae if BP levels are only lowered into the range of slightly below 140/90 mm Hg. Epidemiologic data document that the risk of CVD doubles for every 20/10 mm Hg increment above ~115/75 mm Hg. Currently recommended target-organ protection BP levels for nonhigh-risk patients with hypertension remain well above the upward inflection point for CVD risk (~115/75 mm Hg; Figure 1). Thus, given the extensive clinical database regarding the risks and benefits of pharmacologic treatment and the fact that virtually no unconfounded evidence exists that pharmacologic treatment is harmful in most patients with hypertension, striving to maintain BP levels as close to the upward inflection point (~115/75 mm Hg) for CVD risk with a combination of lifestyle modifications and drug therapies seems intuitively appealing. Nevertheless, attaining and maintaining such a BP level will be more difficult in high-risk patients with hypertension than in their nonhigh-risk counterparts. A qualified recommendation of this nature, however, does not obviate the necessity to prove its validity in clinical end point studies.

**Control of BP Levels**

Thirty-one percent of white, 27% of black, and 41% of Mexican American people with hypertension are unaware of their
condition. Seventy-five percent of people were unaware that they had hypertension, even though their BP was measured by a health professional within the previous year. Approximately 40% were taking a non-BP prescription medicine and the 75% of patients who were unaware that they had hypertension averaged at least 3 clinic visits to a physician’s office a year. Accordingly, better identification of hypertension in our clinical practices seems warranted.

It is also important to identify all concurrent CVD risk factors and to undertake adequate risk stratification of patients before treatment. For example, application of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines would require, at a minimum, that diabetes status be ascertained, that a spot urine albumin to creatinine ratio be obtained, and that serum creatinine be measured so that the glomerular filtration rate can be estimated.

**Therapeutic Inertia**

Therapeutic inertia is lack of practitioner action to intensify anti-hypertensive drug therapy or initiate new antihypertensive drugs for a patient with documented BP elevations. Therapeutic inertia occurs in the majority of hypertension visits that occur in the ambulatory outpatient setting among patients with documented BP elevations. In a 2006 study by Okonofua and colleagues, therapeutic inertia occurred at ~87% of clinic visits when BP was uncontrolled (>140/90 mm Hg). It is important that higher therapeutic inertia scores were linked to significantly less longitudinal BP lowering. Accordingly, patients in the lowest therapeutic inertia quintile were ~33 times more likely than those in the highest quintile to attain BP control. The investigators further estimated that if therapeutic inertia could be avoided in ~30% of visits, BP control rates would increase from 45.1% to 65.9% in this hypertensive cohort.

Therapeutic inertia is not solely the result of the practitioner, but likely represents a complex interaction between the patient and the practitioner. Patients are often reluctant to take either higher doses or additional antihypertensive medications, in part because they mistake BP-related side effects for drug-induced side effects. In clinical practice, patients’ belief that the long-term use of antihypertensive medication is potentially more harmful than persistent BP elevations with less-intense pharmacologic treatment is not uncommon. The practitioner often gets frustrated by seeing limited reductions in BP levels, which may be in part because of the use of suboptimal drug combinations, patient noncompliance, and patient reports of drug-induced side effects. Thus, the practitioner is susceptible to the incessant bargaining that occurs during office visits with patients promising to lose weight, begin exercising, reduce their salt intake, and so on—all so that no increases in antihypertensive drug therapy are prescribed. My impression is that this bargaining and practitioners’ susceptibility to such bargaining is particularly intense when the patient’s goal BP level is almost achieved but still above target.

**Patient Noncompliance**

Patient noncompliance with prescribed antihypertensive drug regimens is very common. High medication adherence (≥80%) compared with intermediate (50%-79%) and low (<50%) medication adherence to a single-pill antihypertensive drug regimen (as estimated by the medication possession ratio) was recently linked to greater BP control—43% for high, 34% for intermediate, and 33% for low medication adherence, respectively, over a 4-year period in 13 U.S. health plans. Furthermore, in this same study, there was a borderline significant inverse relationship between adherence and the number of unique nonantihypertensive drugs, and a strong direct relationship between the mean days of drug supply per pharmacy claim and adherence. The number of unique nonantihypertensive drugs taken per patient was inversely and strongly related to a lower BP control rate.

Patterns of antihypertensive medication nonadherence were reported across 21 studies of once-daily antihypertensive drug treatment using ambulatory electronic monitors. These authors found one half of patients with hypertension discontinued antihypertensive medications within one year, approximately 8% to 10% of scheduled drug doses were missed on any given day, weekend doses were more likely to be missed than weekday doses, and evening doses were more likely to be missed than morning doses. Intriguingly, the quality of execution of the daily drug dosing regimen in the early phase of treatment was a predictor of early discontinuation. There is a complex
aggregate of reasons for patient noncompliance, which relate to patient, physician, and health care system factors. Nevertheless, these data provide some clues to potential strategies controlled by the practitioner that should minimize noncompliance. One easy-to-implement strategy that minimizes the loss of BP control during intermittent noncompliance is to use antihypertensive drugs with prolonged hypotensive effects (preferably effects that extend well beyond the 24-hour dosing interval). This approach should provide some coverage against loss of BP control during the vulnerable period between the missed dose and the next dose of medication taken (Figure 2).

### Optimizing Available Strategies

#### Lifestyle Modifications

Practitioners should always emphasize appropriate lifestyle changes that have shown benefit in lowering BP and/or increasing target-organ protection. The Table displays such lifestyle and behavioral changes. Many, though not all, hypertensive patients are overweight, and the implementation of the suggested lifestyle changes in many hypertensive patients will induce weight loss. At least a few of the recommendations are probably less familiar to the average patient. Calcium intake has been shown to reduce BP levels in persons with low daily intakes of calcium and/or hypovitaminosis D. Natural sources of calcium, such as low-fat dairy products, have been proven more effective than dietary supplements. Emerging data show that augmentation of dietary calcium intake promotes weight loss and lower body fat. Optimizing Available Strategies

When BP levels are > 20/10 mm Hg above normal (per JNC 7) or >15-20/10 mm Hg above normal (per ISHIB), practitioners should recommend the use of multiple antihypertensive drugs. Multiple antihypertensive drugs will be needed to attain and maintain goal BP levels in most hypertensive patients. Use of suboptimal antihypertensive drug regimens has been identified as a major cause of inadequate BP control in patients referred to specialty antihypertensive care settings. Pharmacologic antagonism of the RAAS, which is reviewed in this supplement by Atlas, has shown the most promise for conferring target-organ protection.

#### Pharmacologic Strategies

A major step forward in pharmacologically treating hypertension is to minimize the reliance on monotherapy. In most trials in patients with hypertension, the average BP levels typically remain well above 140/90 mm Hg, even with combination therapy. It is a distinct minority of pharmacologically treated patients with hypertension who will attain their goal BP without the use of multiple antihypertensive drugs.

Combination drug therapy should be embraced with a vengeance. The JNC 7 guidelines and the International Society on Hypertension in Blacks (ISHIB) guidelines on hypertension both comment explicitly on the use of multidrug therapy.

---

**TABLE 1** Lifestyle and Behavioral Changes to Lower Blood Pressure

<table>
<thead>
<tr>
<th>Changes</th>
<th>Interventions</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical activity</strong></td>
<td>Increase</td>
<td>Appropriate aerobic activity should be encouraged. Weight lifting (heavy) can raise blood pressure.</td>
</tr>
<tr>
<td><strong>Diet</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>Decrease</td>
<td>Approximately 2 g (87 mmol) of dietary sodium a day is a good target. Approximately 80% of dietary sodium comes from processed foods.</td>
</tr>
<tr>
<td>Potassium</td>
<td>Increase</td>
<td>Approximately 4.7 g (120 mmol) of dietary potassium a day is recommended by the Institute of Medicine. Fresh fruits and green leafy vegetables are good sources of dietary potassium.</td>
</tr>
<tr>
<td><strong>Lifestyle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Limit</td>
<td>Fewer than 2 drinks (1 oz or 30 mL of ethanol) a day is recommended.</td>
</tr>
<tr>
<td>Smoking</td>
<td>Avoid or quit</td>
<td>Smoking acutely raises blood pressure.</td>
</tr>
</tbody>
</table>
protection that can be statistically disentangled from reductions of BP levels. However, in free-living patients with hypertension who may consume ad libitum daily amounts of dietary sodium, the BP-lowering efficacy of RAAS blockers is attenuated more so than the BP-lowering efficacy of calcium antagonists (and probably diuretics), whereas RAAS blockers, during low dietary sodium intake, lower BP to a similar degree as calcium antagonists. This BP lowering was seen in an examination of the relationship of SBP and urinary sodium excretion, which confirmed that isradipine, a calcium antagonist, decreased BP responsiveness to sodium to a greater degree than either placebo or enalapril, an angiotensin-converting enzyme inhibitor (ACEI). However, it is fortuitous that diuretics and calcium antagonists both augment the reduction of BP levels of RAAS antagonists in high-sodium environments quite well.

Race should be avoided as a criterion on which to base the selection of antihypertensive drug therapy. Diuretics and calcium blockers have been promulgated as meriting favor in blacks, while beta-blockers and RAAS antagonism have been advocated in whites. These recommendations appear to contradict physiologic data that suggest that blacks have greater activation of the RAAS than whites. Furthermore, increasing dietary sodium intake (which undermines BP reduction with RAAS antagonists) consequently suppresses renin but also turns the synthesis of vascular angiotensin II while suppressing the production of nitric oxide. There is strong evidence that despite the greater BP responses of whites compared with those of blacks to monotherapy with a ACEI (for example, the BP response distributions are wide—much wider than the differences in the means of the race-specific response distributions—and these distributions overlap to a very large degree), the addition of either a calcium antagonist or a diuretic to RAAS blockers enhances the BP response and also eliminates racial differences in BP response. Thus, the vast majority of the BP response distribution to RAAS monotherapy is shared between races, rendering this factor a grossly inaccurate predictor of BP responses for individuals of either race targeted. Finally, the use of self-identified race as a criterion for drug selection will prove this research.

**New Therapies**

Because many patients still do not reach their target BP level, there remains an unmet need to find new antihypertensive therapies that are safe, reduce BP effectively, and provide target-organ protection. It appears unlikely that pharmacologic interruption of any physiologic system in isolation is going to reduce BP to a level that will allow most hypertensive patients to attain BP normalization on a single agent. Therefore, newer therapies need to combine well with older therapies, so that they may be effectively integrated into multidrug regimens.

**Direct Renin Inhibitors**

One pharmacologic approach has been targeted at the RAAS, but unlike ACEIs and ARBs, it has a novel mechanism of action. Direct renin inhibitors (DRIs) are the newest antihypertensive drug class on the market in the United States. Aliskiren, the first drug in this class to receive Food and Drug Administration (FDA) approval, is indicated for treatment of hypertension in doses of 150 mg and 300 mg once daily. Aliskiren has a long terminal half-life (24-40 hours) and, after abrupt withdrawal, BP rises very slowly over several weeks back to pretreatment levels. Despite providing blockade of the rate-limiting step in the synthesis of angiotensin II, the addition of an ARB to aliskiren provides incremental BP lowering. The drug is partially metabolized via the cytochrome 3A4 pathway, although approximately one quarter of the absorbed dose is excreted in the urine as the parent drug. There is no need, however, to alter aliskiren dosing in persons with either chronic kidney or liver disease. As with other RAAS blockers, combining aliskiren with diuretics produces a very significant incremental BP response with attenuation of the risk of diuretic-induced hypokalemia, and with a lower incidence of cough and angioedema compared with ACEIs. In an article in this supplement, Pool provides an in-depth review of aliskiren and the clinical utility of this agent.

**Summary**

Control of BP to levels persistently below target levels will require multiple antihypertensive agents in the majority of patients with hypertension. The use of thiazide diuretics and calcium antagonists with RAAS antagonists represents the logical combinations that reduce BP very effectively. Pharmacologic antagonism of the RAAS (ACEIs, ARBs, or DRIs) has shown the most promise for preventing target-organ injury or failure to a degree not solely explained by the reduction of BP levels. Practitioners should attempt to implement multidimensional lifestyle and behavioral changes that will also help reduce BP levels. Antihypertensive agents do not lower risk for all BP-related end points equivalently, even when cuff BP is lowered to a similar degree, but the need for multiple antihypertensive agents to control BP affords the practitioner the ability to use highly effective drug combinations that both reduce BP and protect target organs.

**DISCLOSURES**

Funding from the National Institute of Environmental Health Sciences supported this research.

**REFERENCES**


36. Tekturna (aliskiren) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2007.


