ABSTRACT

OBJECTIVE: This study was conducted to evaluate the relationship between medication compliance and blood pressure (BP) control among members of 13 managed care organizations with essential hypertension (HTN) who received antihypertensive monotherapy for at least 3 pharmacy claims prior to the blood pressure measurement.

METHODS: This was a retrospective review of medical and pharmacy claims over a 4-year period (1999-2002) from 13 U.S. health plans. Data were collected by trained health professionals from randomly selected patient medical records per Health Plan Employer Data and Information Set (HEDIS) technical specifications. Patients were selected if they (1) had received monotherapy or fixed-dose combination therapy (administered in one tablet or capsule) during the time BP was measured (thus those with no BP drug therapy were excluded); (2) had received 3 or more antihypertensive pharmacy claims for the antihypertensive drug therapy prior to BP measurement; and (3) had one or more antihypertensive pharmacy claims after BP was measured. Control of BP was defined according to guidelines of the Sixth Report of the Joint National Committee (JNC 6) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (<140/90 mm Hg, or <130/85 mm Hg for patients with diabetes). Medication adherence was measured using the medication possession ratio (MPR), and MPR was used to classify patients into 3 adherence levels: high (80%-100%), medium (50%-79%), and low (<50%). The relationship between medication adherence and BP control was assessed using a logistic regression model.

RESULTS: There were 1,017,181 patients with a diagnosis of HTN in medical claims data from which 10,734 (10.6%) were randomly selected for chart review. There were 1,032 patients (9.6%) in the sample who had a diagnosis of HTN but who were excluded because they had no HTN drug therapy. Of the total 9,894 patients (92.2%) who were excluded from the sample, 3,029 patients (28.2%) met all other inclusion criteria but were receiving more than one HTN drug. Of the 840 patients on HTN monotherapy, the mean age was 59 ± 12.2 years; 422 (50%) were women, 16% had diabetes, and 43% had dyslipidemia. The monotherapy HTN drug was an angiotensin-converting enzyme inhibitor (27% of patients), calcium channel blocker (22%), beta-blocker (20%), or diuretic (11%). Of the 840 patients, 629 (74.8%) were determined to have high medication adherence, 165 (19.6%) had medium adherence, and 46 (5.5%) had low adherence. Approximately 270 (43%) of high adherence patients achieved BP control compared with 56 (34%) and 15 (33%) patients with medium and low adherence, respectively. High-adherence patients were 45% more likely to achieve BP control than those with medium or low compliance after controlling for age, gender, and comorbidities (odds ratio = 1.45; P = 0.026).

CONCLUSION: These results demonstrate that 75% of these health plan members with a diagnosis of essential HTN who were selected for receipt of at least 4 pharmacy claims for HTN monotherapy exhibited high medication adherence. However, only 43% of high-adherence patients attained their target (JNC 6) blood pressure goal compared with 33% to 34% of patients with medium or low adherence to antihypertensive monotherapy.

KEYWORDS: Antihypertensive therapy, Compliance, Medication possession ratio, Hypertension

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Cardiovascular disease, the leading cause of death and disability in the United States, is associated with inadequate blood pressure (BP) control. The relationship between BP and risk of cardiovascular events is positive, continuous, consistent, and independent of other risk factors. Unfortunately, BP control is particularly poor among hypertensive patients at the highest risk for cardiovascular events, including patients with diabetes and older patients with systolic hypertension (HTN).

Randomized controlled trials conducted over the last 4 decades have provided evidence to support the effectiveness of BP lowering to reduce the risks of cardiovascular disease. Pharmacologic treatment of high BP can reduce the risk of stroke by 30% to 40% and myocardial infarction (MI) by 20% to 25%. Failure to reach BP treatment goals contributes to the burden of HTN complications. Results of the Cardiovascular Health Study suggest that undertreating systolic BP of >140 mm Hg accounts for 34% of strokes and 22% of MIs in older adults. Recent population data indicate that only 31% of all hypertensive individuals are controlled to <140/90 mm Hg. Thus, almost 70% of the more than 50 million Americans with high BP are at increased risk of cardiovascular complications due to the failure to reach goal BP.

Although poor BP control can be attributed to several factors, one pivotal reason is the problem of long-term patient compliance with therapy. Lack of compliance with BP-lowering medication is a major reason for poor control of BP. Reasons for poor compliance vary. Patients with high BP may fail to take their medication because of the chronic nature of HTN and its absence of overt symptoms; other reasons that have been studied include the adverse effects of medication, complicated drug
Relationship of Blood Pressure Control to Adherence With Antihypertensive Monotherapy in 13 Managed Care Organizations

### TABLE 1 Sample Selection*

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Number (%) of Patients Dropped</th>
<th>Number (%) of Patients Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomly selected for chart review analysis*</td>
<td>–</td>
<td>10,734 (100)</td>
</tr>
<tr>
<td>Patients with both pharmacy and medical claims†</td>
<td>1,032 (9.6)</td>
<td>9,702 (90.4)</td>
</tr>
<tr>
<td>Patients with pharmacy claims overlapping BP date‡</td>
<td>5,010 (46.7)</td>
<td>4,692 (43.7)</td>
</tr>
<tr>
<td>Patients with 3 or more antihypertensive Rxs pre-BP date</td>
<td>757 (7.1)</td>
<td>3,935 (36.6)</td>
</tr>
<tr>
<td>Patients with 1 or more antihypertensive Rx(s) post-BP date</td>
<td>66 (0.6)</td>
<td>3,869 (36.0)</td>
</tr>
<tr>
<td>Patients receiving antihypertensive monotherapy</td>
<td>3,029 (28.2)</td>
<td>840 (7.8)</td>
</tr>
</tbody>
</table>

* 1,017,181 patients with an HTN diagnosis (ICD-9-CM code 401.x for essential hypertension) in medical claims data from which 10,734 (10.6%) were randomly selected for chart review.
† Only 1 medical claim with an HTN diagnosis was required.
‡ June 1, 1998, was the earliest date of service for a pharmacy claim and the latest date was September 30, 2002.

BP = blood pressure; ICD-9-CM = International Classification of Diseases, Ninth Revision (ICD-9) code indicating the diagnosis of essential HTN (401.x) during the first 6 months of the measurement year. To be included in this study, there also had to be the notation of a diagnosis of HTN in the medical record on or before the first 6 months of the measurement year as defined by the HEDIS HTN performance measure. The HEDIS measure requires medical record review to confirm the diagnosis of HTN and to evaluate BP control. A total of 1,017,181 patients were identified with a diagnosis of essential HTN in the medical claims. By plan, patients were randomly selected for chart review to produce a representative sample of patients for each plan via a random number process generated using SAS Statistical Software version 8.0 (SAS Institute Inc., Cary, NC). This process ensured no patient or health characteristics influenced the selection of patients for chart review.

Records were included from patients who (1) had received antihypertensive monotherapy (defined as 1 agent) or fixed-dose combination (administered in 1 tablet or capsule) during the time BP was measured (patients switching therapy but maintaining monotherapy status remained in the study); (2) had received 3 or more antihypertensive pharmacy claims prior to BP measurement in the 270 days preceding BP measurement; and (3) had one or more antihypertensive pharmacy claims after BP was measured (Table 1). In other words, all patients included in the final analysis had received at least 4 pharmacy claims for HTN monotherapy. Only patients who received monotherapy (including fixed-dose combination) were included, in an attempt to reduce the confounding influence of HTN severity and permit selection of a more homogeneous population with regard to HTN severity.

Also, the inclusion of monotherapy patients simplified measurement of therapy compliance and increased confidence in a causal relationship between compliance and BP control. Inclusion of patients receiving other regimens such as dual therapy may increase the external validity, but little “real-world” research exists examining the association between compliance and BP control. Therefore, a simplified approach in patients receiving monotherapy was done to evaluate if any association existed. A single BP value was used from each patient who
fulfilled all 3 criteria, and the date of the BP measurement was selected to ensure that it occurred during the compliance measurement period. BP measurements were obtained from readings recorded in medical charts either by nurses or physicians. Control of BP was defined according to the then-current guidelines of the Sixth Report of the Joint National Committee (JNC 6) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (<140/90 mm Hg, and <130/85 mm Hg for patients with diabetes). The use of BP controls as defined in the JNC 6 guidelines permitted a continuous measure of BP to be converted into a dichotomous variable representing control: yes or no. All diagnosis code fields were reviewed, and patients with codes for diabetes, hyperlipidemia, and heart failure also were identified.

**Medication Possession Ratio and Other Measures of Interest**

Medication adherence rates were generated using the MPR, defined as the supply of medication in days divided by the total number of days in the study period (actual treatment days), then multiplied by 100 to convert to a percentage. This definition of MPR is similar to that employed in previous studies. The numerator was the sum of all days supplied regardless of whether prescriptions involved overlapping days. The number of days was counted beginning from the fill date of the patient’s first pharmacy claim to the fill date of the patient’s last pharmacy claim. The days supply of the last observed pharmacy claim was not included in the summation of the supply of medication. As no antihypertensive pharmacy claim activity occurred after the last observed pharmacy claim, adherence to the last prescription could not be determined. While electronic measurement of compliance is often done in prospective studies, MPR is a well-accepted methodology to measure medication use in research with administrative pharmacy claims. Adherence was capped at 100%; i.e., MPR values greater than 1.0 were reduced to 1.0.

The MPR measure of adherence can be influenced by use of 90-day and larger supplies from mail-service pharmacies. Fewer than 9% of all pharmacy claims had supply quantities ≥90 days. Patients were categorized into 3 adherence groups: high (80%-100%), medium (50%-79%), and low (<50%). These categories were specified a priori and based on a study by Psaty et al. that indicated that patients who took less than 80% of their hypertensive medication were at a 4-fold risk for acute cardiac events than patients who took 80% or more of their medications. In addition, several other studies have used 80% as a cut-off point when assessing compliance in HTN and other disease states as well. Adherence was capped at 100%; i.e., MPR values greater than 1.0 were reduced to 1.0.

Potential factors associated with adherence in this study included age, gender, prescription count of nonantihypertensive medications, and severity of illness adjusted according to the Charlson Comorbidity Index. The Charlson index contains 19 categories of comorbidities and includes scores from 0 to ≥6, according to the absence or presence of comorbid disorders, which are indicated by ICD-9 codes and was assessed up to 270 days prior to the date of the BP recording.

### Statistical Analysis

The relationship between BP control and medication adherence was assessed using a logistic regression model. In this regression analysis, BP control was modeled as a function of adherence controlling for age, gender, Charlson index, HTN medication class, and count of the number of non-HTN medications. One indicator variable for adherence was constructed whereby those subjects with an MPR of at least 80% were compared with those with an MPR of less than 80%. Three indicator variables were for HTN medication class whereby ACE inhibitors, beta-blockers, and calcium channel blockers were compared with all other HTN medication classes (i.e., diuretics, alpha-blockers, fixed-dose combination). All statistical analyses were performed using the SAS Statistical Software version 8.0 (SAS Institute Inc., Cary, NC). The a priori level of significance was α < .05.

### Results

The characteristics of the managed care study population (N = 840) are summarized in Table 2. Patients had a mean age of 59 ± 12.2 years (range, 22-93 years). Most patients had uncontrolled BP (60%) according to JNC 6 guidelines. The majority of patients were in the high-adherence category with a mean MPR of 87%. The most commonly prescribed antihypertensive agents were angiotensin-converting enzyme (ACE) inhibitors.
Discussion

These results suggest that adherence to antihypertensive medications is associated with a higher proportion of HTN patients who reach target BP control. To our knowledge, no other research has established an association between medication adherence and BP control in a real-world setting. In addition, this study begins to explore the magnitude of this association. Such assessments are necessary and provide valuable data for groups such as the American Heart Association's Task Force on Compliance. In fact, this task force was charged with determining "if sufficient data exist to make specific recommendations about compliance."27 Control to the target goal of <140/90 mm Hg (<130/85 mm Hg for patients with diabetes), according JNC 6 guidelines in effect at the time that these data were collected, was achieved in 43% of high-adherence patients compared with BP control rates of only 34% and 33% for medium and low adherence, respectively. Prior to adjustment, these ratios were not significant (P = 0.06).

Of note is the finding that a higher number of medications other than the HTN monotherapy was associated with a lower likelihood of reaching goal BP. One explanation for this finding is the difference in severity scores of the patients—the Charlson index score was apparently higher in the low-adherence group, but P = 0.12 for the comparison (Table 3). However, this was controlled in the regression analysis, using the Charlson index. In a systematic review of randomized controlled trials of interventions to improve compliance with BP-lowering medication,8 it was shown that increasing the complexity of a medication regimen results in decreased medication compliance. In 7 of 9 studies included in the review, simplifying the dosing regimen was found to increase compliance; specifically, reducing the number of daily doses appeared related to higher compliance with antihypertensive medication. Other studies have shown that a higher number of total medications is related to lower patient compliance and that both the class of medication prescribed and the number of tablets taken each day are important factors in patient compliance.25-33 In this study, patients were taking an average of at least 6 distinct nonantihypertensive medications.

Blood pressure control is potentially determined by multiple factors, including the underlying pathophysiology of HTN; age, severity of disease, health habits, and presence of comorbid illness; compliance with medication; and the impact of health care systems.34 Most Americans with poor BP control have health insurance coverage, availability, and access to medical care.3,35

Several reports suggest that a major factor in inadequate BP control is clinical inertia, or the physician's failure to titrate or combine medications when seeing a patient with uncontrolled BP control after BP measurement (SD) P < 0.001 (Table 3).

No. of patients with BP control* (%) 270 (42.9%) 56 (33.9%) 15 (32.6%) P = 0.06
Charlson index score (SD) 0.78 [1.52] 0.55 [1.34] 0.97 [1.85] P = 0.12
Mean no. of unique, non-HTN agents (SD) 5.8 [4.5] 6.0 [4.5] 7.5 [6.3] P = 0.06
No. of patients with diabetes (%) 97 (15.4%) 28 (17.0%) 7 (15.2%) P = 0.92
No. of patients with dyslipidemia (%) 276 (43.9%) 73 (44.2%) 13 (28.3%) P = 0.11
Mean no. of patients with heart failure (%) 7 (1.1%) 3 (1.8%) 0 (0%) P = 0.57
Mean no. of HTN pharmacy claims before BP measurement (SD) 10.6 [7.0] 8.7 [4.5] 6.2 [3.1] P < 0.001
Mean no. of HTN pharmacy claims after BP measurement (SD) 6.5 [6.5] 5.2 [4.3] 2.8 [2.1] P < 0.001
Mean MPR (SD) 94.8 [5.7] 69.1 [8.4] 39.1 [9.4] P < 0.001
Mean days supply per pharmacy claim (SD) 39.4 [21.2] 32.8 [12.6] 30.2 [8.9] P < 0.001

* Blood pressure control defined by the Sixth Report of the Joint National Committee (JNC 6) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (<140/90 mm Hg, or <130/85 mm Hg for patients with diabetes).
BP = blood pressure; HTN = hypertension; MPR = medication possession ratio.

Inhibitors, calcium channel blockers (CCBs), beta-blockers, and diuretics. Table 3 summarizes the severity measures by MPR category. Overall, patients were generally healthy, with an overall Charlson index score of <1.

Blood pressure was controlled to JNC 6 goal in 270 patients (42.9%) in the high-adherence group versus 56 patients (33.9%) in the medium-adherence group and 15 patients (32.6%) in the low-adherence group (P = 0.06, Table 3 and Figure 1). Highly adherent patients were 45% more likely to achieve BP control than patients with medium or low adherence to HTN monotherapy, after controlling for age, gender, HTN medication class, and comorbidities (odds ratio [OR] = 1.45; P = 0.026). Additionally, a higher total number of nonhypertensive medications was associated with a lower rate of BP control (OR = 0.95; P = 0.007, Table 4).

The high HTN medication adherence group received a higher proportion of pharmacy claims with a larger average days supply. The mean days supply per pharmacy claims was 39.4 for the high-adherence group versus 32.8 days for the medium-adherence group and 30.2 days for the low-adherence group (P < 0.001, Table 3).

### Table 3: Patient Characteristics and Pharmacy Claims by MPR Adherence Category

<table>
<thead>
<tr>
<th>MPR Category Based on MPR</th>
<th>High MPR ≥ 0.80 (n = 629)</th>
<th>Medium MPR 0.50–0.79 (n = 165)</th>
<th>Low MPR &lt; 0.50 (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with BP control* (%)</td>
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<td>6.0 [4.5]</td>
<td>7.5 [6.3]</td>
</tr>
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<td>No. of patients with diabetes (%)</td>
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<td>7 (15.2%)</td>
</tr>
<tr>
<td>No. of patients with dyslipidemia (%)</td>
<td>276 (43.9%)</td>
<td>73 (44.2%)</td>
<td>13 (28.3%)</td>
</tr>
<tr>
<td>No. of patients with heart failure (%)</td>
<td>7 (1.1%)</td>
<td>3 (1.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Mean no. of HTN pharmacy claims before BP measurement (SD)</td>
<td>10.6 [7.0]</td>
<td>8.7 [4.5]</td>
<td>6.2 [3.1]</td>
</tr>
<tr>
<td>Mean no. of HTN pharmacy claims after BP measurement (SD)</td>
<td>6.5 [6.5]</td>
<td>5.2 [4.3]</td>
<td>2.8 [2.1]</td>
</tr>
<tr>
<td>Mean days supply per pharmacy claim (SD)</td>
<td>39.4 [21.2]</td>
<td>32.8 [12.6]</td>
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</tr>
</tbody>
</table>
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BP $^2,^3,^9$ It is of interest to compare the BP control rate in this study with that reported in a recent, similarly designed study using a retrospective review of patient records and refill history, in which only 34.8% of treatment-compliant, hypertensive, male veterans had BP levels $<140/90$ mm Hg.$^7$ In that study, the percentage of patients whose BP was controlled increased in proportion to the number of antihypertensive drugs taken, with the highest BP control seen in nondiabetic patients receiving 2 or more agents and in diabetic patients receiving 3 or more antihypertensive agents. Furthermore, there was a strong inverse relationship between the number of antihypertensive drugs and systolic BP readings ($r^2$ [coefficient of determination] = .87; $P = 0.001$).$^7$

The JNC 7 report lowered the blood pressure goal for diabetics even further, to $<130/80$ mm Hg.$^2$ These low BP goals are difficult to achieve, especially in patients with diabetes. Results of recent, large clinical trials have shown that monotherapy is unable to bring BP to goal levels in most patients.$^4$ In the largest antihypertensive drug trial ever conducted, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),$^{38}$ only 30% of patients achieved BP $<140/90$ mm Hg with monotherapy. This evidence, together with that from other published studies, has increased the recognition among practitioners that goal BP is achieved in the majority of patients only when 2 or more antihypertensive medications are employed.$^2,^9$ One proposed option for improving BP control and patient compliance is the use of fixed-dose combination antihypertensive therapy.$^2,^15,^40$ In a recent study, subjects receiving a once-daily, fixed-dose combination of an ACE inhibitor and a dihydropyridine CCB demonstrated significantly greater compliance with their medication regimen, compared with subjects receiving a similar regimen containing an ACE inhibitor and a dihydropyridine CCB as separate drugs.$^{11}$ Wogen et al., in a previous study published in *JMCP*, found higher adherence with the ARB, valsartan, compared with amlodipine or lisinopril.$^{12}$

Approximately half of the patients in the present study were taking either ACE inhibitors or CCBs. The proportion of patients taking angiotensin receptor blockers (ARBs) was small (3%).

Limitations

Foremost among the limitations of this study was the use of only one BP measurement. Second, the potential influence of mail-service pharmacy on the measure of medication adherence was not considered in the study design, and the proportion of mail-service claims was not measured or reported in the results. The high-adherence group in this study received an average 39.4 days supply per HTN pharmacy claim compared with 32.8 days per HTN claim in the medium-adherence group and 30.2 days per HTN in the low-adherence group ($P < 0.001$).

Third, due to the retrospective nature of the study, some potential confounding factors were not available for the model, such as smoking, family history of cardiovascular disease, socioeconomic status, and other risk factors. Fourth, this analysis was limited to patients receiving monotherapy, and the results may not be generalizable to patients receiving common regimens such as dual or triple therapy to control BP. Fifth, formulary status and copayment tier were not determined in the

![FIGURE 1](https://example.com/figure1.png)

**FIGURE 1** Blood Pressure Control According to JNC 6 by Category of Medication Adherence

$^*$ $P = 0.06$ prior to adjustment; $P = 0.026$ in regression analysis.

The level of blood pressure control was 43% in the 629 patients who were highly compliant versus 34% for 165 patients with medium compliance and 33% in 46 patients with low compliance.


![TABLE 4](https://example.com/table4.png)

**TABLE 4** Blood Pressure Control—Logistic Regression Model Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High adherence*</td>
<td>1.45</td>
<td>1.04-2.02</td>
<td>0.026</td>
</tr>
<tr>
<td>Female</td>
<td>1.18</td>
<td>0.88-1.59</td>
<td>0.27</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.98-1.00</td>
<td>0.10</td>
</tr>
<tr>
<td>ACE inhibitor†</td>
<td>0.79</td>
<td>0.54-1.15</td>
<td>0.23</td>
</tr>
<tr>
<td>Beta-blocker†</td>
<td>0.80</td>
<td>0.53-1.20</td>
<td>0.28</td>
</tr>
<tr>
<td>Calcium channel blocker†</td>
<td>0.72</td>
<td>0.49-1.05</td>
<td>0.10</td>
</tr>
<tr>
<td>Charlson index</td>
<td>1.01</td>
<td>0.91-1.12</td>
<td>0.82</td>
</tr>
<tr>
<td>Number of nonhypertensive medications</td>
<td>0.95</td>
<td>0.92-0.98</td>
<td>0.007</td>
</tr>
</tbody>
</table>

* Reference group was medium and low adherence.
† Reference group was all other HTN classes (e.g., diuretics, fixed-dose combination, alpha-blocker).

ACE = angiotensin-converting enzyme; HTN = hypertension.
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present study and may influence measurement of medication adherence using administrative claims data.43

While the present study focused on monotherapy (including 10 patients [1.2%] who received fixed-dose combination therapy), to reduce the complexity in measuring medication adherence, the results show that blood pressure control was attained in only 43% of patients who had MPR values ≥80%. This suggests that these patients were not dosed properly and many probably required more than monotherapy to attain BP goal. This supports JNC 7 guidelines, which recommend combination therapy for patients with stage 2 HTN without compelling indications (e.g., heart failure, diabetes, chronic kidney disease). In addition, combination therapy should be considered for patients with stage 1 HTN without compelling indications and for patients with compelling indications regardless of stage. Even though many of these patients may have been treated inappropriately with a single HTN agent, the results still indicate that greater BP control is associated with higher medication adherence as measured by the MPR.

Conclusion

Across 13 MCOs, 75% of members who received at least 4 pharmacy claims for an antihypertensive medication during the study period exhibited high medication adherence with antihypertensive monotherapy, but only 43% of high-adherence patients attained their target blood pressure goal compared with approximately one third of patients with either medium or low adherence with antihypertensive monotherapy.

DISCLOSURES

Funding for this research was provided by Novartis Pharmaceuticals Corporation and was obtained by author Thomas J. Bramley. Author Feride Frech-Tamas is an employee of Novartis Pharmaceuticals Corporation. The other authors disclose no potential bias or conflict of interest relating to this article.

An abstract of this paper was presented at the 19th Annual Scientific Meeting of the American Society of Hypertension, New York, New York, May 22, 2004, and published in The American Journal of Hypertension. (Am J Hypertens. 2004;17(5 part 2):222A.) Bramley served as principal author of the study. Study concept and design were contributed primarily by Bramley, with input from authors Philip P Garbino, Brian S. Nightengale, and Frech-Tamas. Data collection was the work of Bramley; data interpretation was the work of all authors. Drafting of the manuscript was primarily the work of Bramley; with input from Nightengale, Frech-Tamas, and Garbino, its revision was the work of all authors.

REFERENCES


