RACIAL DIFFERENCES IN MEDICATION COMPLIANCE AND HEALTHCARE UTILIZATION AMONG HYPERTENSIVE MEDICAID RECIPIENTS: FIXED-DOSE VS FREE-COMBINATION TREATMENT

Michael Dickson, PhD; Craig A. Plauschinat, PharmD, MPH

Objective: To assess compliance with antihypertensive therapy and healthcare utilization among African American and White Medicaid recipients who are receiving fixed-dose combination amlodipine besylate/benazepril HCl or a dihydropyridine calcium channel blocker plus an angiotensin-converting enzyme inhibitor prescribed as separate agents (free-combination).

Design: Longitudinal, retrospective, cohort analysis of South Carolina Medicaid claims for the years 1997 through 2002. Followup was 12 months from the index date, defined as the first prescription dispensing date for a study drug.

Setting and Participants: South Carolina Medicaid beneficiaries receiving fixed-dose ($n=3363$) and free-combination ($n=713$) therapy, including 3016 African Americans and 1060 White patients.

Main Outcome Measures: Compliance was defined as the total days' supply of drug (excluding last prescription fill) divided by the length of followup; healthcare utilization included cost and number of claims associated with ambulatory services, hospital care, and prescription drugs.

Results: The cohort ($N=4076$) was 74.0% African American; mean age was 62.2 years. Compliance was significantly greater in patients who received fixed-dose therapy than in those who received free-combination therapy (58.6% vs 48.1%; $P<.05$). The average total cost of care was lower for the fixed-dose group ($4605) than for the free-combination group ($8531). African Americans and Whites were equally likely to receive the fixed-dose combination. However, compliance was lower among African American patients than among White patients (55% vs 61% respectively; $P<.05$). Costs and claims for ambulatory and hospital services were higher for African American patients, whereas drug costs and claims were higher for White patients.

Conclusion: Fixed-dose amlodipine besylate/benazepril HCl was associated with higher compliance rates than was free-combination therapy, independent of race. Lower compliance rates among African American patients may have contributed to the higher healthcare resource use and costs observed. Efforts to enhance medication compliance tailored to African Americans may improve outcomes and reduce costs in this high-risk population. (*Ethn Dis*. 2008;18:204–209)

Key Words: African American, Amlodipine, Angiotensin-converting Enzyme Inhibitor, Antihypertensive Therapy, Benazepril, Compliance, Dihydropyridine Calcium Channel Blocker, Hypertension, Medicaid

INTRODUCTION

Preventable differences in cardiovascular disease (CVD) and its associated risk factors across race/ethnicity, sex, educational level, socioeconomic status, and geographic location remain pervasive in the United States.[1] The prevalence of hypertension is high among African Americans independent of sex or educational level, and CVD mortality at all ages tends to be highest in African Americans. African Americans develop hypertension earlier and more frequently than do White Americans, and have higher systolic blood pressure levels. As a result of these and other contributing factors, African Americans have a greater risk of both nonfatal and fatal stroke, CVD death, and end-stage renal disease.[2,3] An overarching goal of *Healthy People 2010*, the nation's health objectives and indicators, is the elimination of such health disparities among segments of the US population.[4]

The prevalence of hypertension increased substantially among both African Americans and White Americans over the last decade and remains significantly higher in African Americans despite greater hypertension awareness and use of antihypertensive medication.[5,6] According to recent data from the National Health and Nutrition Examination Survey, 41.4% of African Americans have hypertension, compared with 28.1% of White Americans.[6] In the group of African Americans aged ≥60 years, the proportion of persons with hypertension reaches 75% of men and 82% of women, compared with 57% and 71% of White men and women.[7] Rates of antihypertensive medication use are higher among African Americans than Whites, driven by higher rates among African American women, yet blood pressure control rates remain significantly lower among African Americans; less than half of treated patients achieve blood pressure goals.[6]

Patient compliance with prescribed medications affects blood pressure control, and persistence with antihypertensive drug therapy tends to decline over time…

Patient compliance with prescribed medications affects blood pressure control, and persistence with antihypertensive drug therapy tends to decline over time, which may be related in part to the class of initial antihypertensive agent prescribed and its tolerability.[8–10] Regimen complexity, dosing frequency, number of concomitant medications, and changes in therapeutic regimen are among several factors identified as contributing to lower rates of compliance and blood pressure control. In a small study of African American patients conducted in an urban setting, barriers to compliance with antihypertensive therapy included patient-specific issues, such as negative perceptions about medications; treatment-related factors, such as side effects, inconvenience, logistics, and cost; and disease-related factors, such as lack of symptoms

From the College of Pharmacy, University of South Carolina, Columbia, South Carolina (MD); Novartis Pharmaceuticals, East Hanover, New Jersey (CAP), USA.

Address correspondence and reprint requests to: Michael Dickson; University of South Carolina; College of Pharmacy; Columbia, SC 29208; 803-777-7900; 803-777-2820 (fax); Dickson@cop.sc.edu

of hypertension.[11] A physician-related factor that can affect blood pressure control is a lack of appropriately aggressive treatment to achieve recommended blood pressure targets.[12,13]

As most patients require two or more antihypertensive agents to reach their goal blood pressure[3]—particularly among those at high risk of cardiovascular events—simpler regimens, fewer doses, less frequent administration, and use of well-tolerated therapies are strategies recommended to improve patient compliance with antihypertensive therapy.[14,15] In addition to the potential for improved outcomes with long-term use, the continuous use of antihypertensive therapy has been associated with lower healthcare costs in a Medicaid population.[16] A study of South Carolina Medicaid claims found that fixed-dose combination antihypertensive therapy was associated with higher compliance rates, lower total costs, and fewer total claims than were the component therapies prescribed as separate drugs.[17] These results formed the basis of the current analysis to assess differences in compliance with combination antihypertensive therapy and utilization of healthcare resources according to subgroups by race in a predominantly African American Medicaid population.

The objectives of this study, therefore, were to compare rates of compliance and healthcare resource utilization (costs and claims) among African American and White hypertensive patients treated with a fixed-dose combination of amlodipine besylate/benazepril HCl vs a dihydropyridine calcium channel blocker (DHP-CCB) plus angiotensin-converting enzyme inhibitor (ACEI) prescribed as separate agents (free-combination).

METHODS

Study Design

This was a longitudinal, retrospective, cohort study using the South Carolina Medicaid database for the period 1997 through 2002. Assessment of healthcare utilization included average cost and number of claims for ambulatory care, hospital care, prescription drugs, and Medicare crossover claims during the follow-up period. Although patients may have had claims in more than one year during the study period, each patient was included only once and followed for 12 months (the follow-up period) from the initial prescription dispensing date (the index date). All personal identifiers were removed before data analyses to protect the confidentiality of study participants in conformance with the Health Insurance Portability and Accountability Act. Appropriate institutional review board approval was obtained.

Patient Selection

Patients were included if they were $\geq$18 but $<$100 years of age on the index date, had received at least two prescriptions for study drugs in one of the study selection years (1997 through 2001), and had at least 12 months of Medicaid continuous eligibility after the index date. Patients were excluded if they had $>$180 days of hospitalization, $<$30 days of study drug supply, or any nursing home claims during the 12-month follow-up period.

The sample consisted of Medicaid beneficiaries who received medical care services during the study years. Medicaid beneficiaries obtain care largely from private-sector healthcare providers (physicians, hospitals, pharmacies, etc) and may be asked to make a modest copayment for services. Providers submit claims to the state Medicaid program to receive payment for the services rendered. Medicaid beneficiaries do not file claims, only the providers.

Study Cohorts

Two cohorts were defined by their use of antihypertensive therapy: a fixed-dose combination group of patients prescribed amlodipine besylate/benazepril HCl and a free-combination group prescribed any combination of a DHP-CCB plus an ACEI as separate agents. DHP-CCBs included amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, and nisoldipine; ACEIs included benazepril, captopril, enalapril, lisinopril, quinapril, and ramipril. Patients taking non-DHP-CCBs were not included in the free-combination group.

To remain in the fixed-dose combination group, patients could not have switched to another ACEI plus DHP-CCB during the follow-up period. Patients in the free-combination group could switch among ACEIs and DHP-CCBs but could not have used a fixed-dose combination of amlodipine besylate/benazepril HCl or other fixed-dose antihypertensive combination product at any time during the follow-up period. For patients in the free-combination group, the dispensing dates for the two drugs could be a maximum of 30 days apart, and the index date was the date of initiation of the first antihypertensive agent.

Outcome Variables

Outcome variables included medication possession ratio (MPR), used as a measure of compliance, and average total cost of care. MPR was defined as the percentage of days that a patient had the study drug(s) available during the one-year follow-up period, excluding the last prescription fill. MPR is one of a few commonly used metrics for measuring medication adherence with pharmacy records. It is used in this study because it is the most generic of adherence measures.[18,19] The number of hospitalization days, if any, was subtracted from the number of days of drug supply (numerator) and the number of days of follow-up (denominator) to account for non-use of drug in hospital and possible prescription changes upon discharge. For patients in the free-combination group, days of

Table 1. Demographic characteristics of South Carolina Medicaid recipients, 1997–2002

Characteristic	Fixed-dose Combination (*n*=3363)	Free-Combination (*n*=713)	Total (*N*=4076)
Age, mean ± standard deviation	61.7±15.9	63.9±15.1	62.2±15.7
Female, n (%)	2505 (74.5)	538 (75.4)	3043 (74.7)
African American, n (%)	2448 (72.8)	568 (79.6)	3016 (74.0)
Urban resident, n (%)	2986 (88.8)	644 (90.4)	3630 (89.1)
Chronic disease score, mean ± standard deviation	5.0±2.5	6.1±2.4	5.3±2.5

drug possession were counted only if both drugs were available on the same day. Total cost of care was defined as the sum of payments for Medicaid claims for ambulatory care (HCFA 1500 claims), hospital care claims (UB-92 claims), prescription drug claims, and Medicare crossover claims. The average monthly costs and claims for each service were calculated for both treatment groups.

Statistical Methods

A logistic regression using pre-index period data (from the one-year period before the index date) was used to calculate a propensity score for each patient to control for selection bias resulting from the nonrandom assignment to treatment groups and to account for differences in prior use of antihypertensive drug therapy.[20] Propensity scores are commonly used in retrospective studies where randomization of subjects to groups is not possible. A single variable is created that represents the probability a subject will be in the treatment group (in this case the fixed-dose group). The propensity score combines variance from all the variables conceptually important in determining a subject's group. Variables included in the propensity score were demographics (age, sex, race, county of residence), chronic disease score as a measure of co-morbidities and to provide an indication of overall medical condition,[21] percentage of ambulatory visits to cardiac specialists for CVD diagnoses, average total cost and number of claims for each type of service included in the study, average monthly expenditure for other cardiovascular prescriptions (non-study drugs), and average monthly expenditure for the fixed-dose and free-combination study drugs. Medicare crossover claims for dually eligible individuals included both Part A (hospital) and Part B (outpatient) claims, which were separated into their respective components. Each of these variables was standardized by the number of months of pre-period eligibility to control for potential differences in eligibility in the pre-index period. Race, recorded by a healthcare professional, was dichotomized into White and African American, but the latter group included a small percentage of unknowns (4.6%). Experience has shown that when race for this group has been resolved, they are most often African American.

Patient-level data were used to calculate an MPR for each patient. A two-sample *t* test was used to compare compliance rates between the fixed-dose and free-combination groups. Multivariate analysis was performed to assess the relationship between compliance and total healthcare costs, and to assess the relationship between race and total healthcare costs and claims for service. For example, an ordinary least squares regression was used to explain variance in the log of total healthcare cost associated with adherence (MPR), while controlling for the potentially confounding variables of treatment group (fixed-dose vs free-combination), chronic disease score, race (African American or White), sex, year selected for the study, and propensity score. The dependent variable in this regression is the log of total healthcare cost because cost data are not normally distributed. In the same way, the regression gives an estimate of the effect of treatment group on the total cost of care while controlling for all other effects. All data management and statistical analyses were performed by using SAS, version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

A total of 4076 Medicaid recipients ≥18 years of age were included in the study, including 3363 in the fixed-dose combination group and 713 in the free-combination group (Table 1). The demographics of fixed-dose and free-combination groups were similar, although the number receiving fixed-dose combination therapy was nearly five times greater.

Compliance

Overall compliance was significantly higher for patients receiving the fixed-dose combination than for those receiving the free-combination (58.6% and 48.1, respectively; $P<.05$). African Americans were as likely to receive the fixed-dose combination as Whites (45% vs 43%, respectively). Overall, however, the MPR for African American patients was significantly lower than for Whites (55% vs 61%, respectively; $P<.05$).

Healthcare Costs and Claims

The average total cost of care (based on ambulatory care, hospital care, prescription drugs, and other costs, including Medicare crossover claims) for patients prescribed the fixed-dose combination was $4605, compared with $8531 for patients prescribed free-

combination therapy. Each category of expenditure was lower with fixed-dose versus free-combination therapy; hospital costs were 70% lower, drug costs 27% lower, and ambulatory costs 38% lower with the fixed-dose combination.

Mean ambulatory and hospital costs and claims were higher for African American patients than for White patients, whereas mean drug costs and claims were higher for White patients than for African American patients (Table 2). Because the multivariate regression controls for other variables, the results in Table 3 are more informative on the relationship between adherence and total cost of care. The same can be said for the relationship of race to total cost of care. In the regression on the log of total cost of care, the variables for race and sex were not significant (Table 3). However, year of selection, chronic disease score, MPR, and treatment group were all significant. Overall treatment costs appear to decrease modestly over time (−3.1%), a greater burden of chronic diseases tends to increase cost of care (20.5%), and a higher compliance rate is associated with higher cost of care (each 1 percentage point increase in MPR=0.71% increase in total cost). Use of fixed-dose therapy was associated with lower total cost (−24.4%). These values are derived from the coefficients reported in Table 3, which are adjusted because the dependent variable is logged. As these are not standardized regression coefficients, it is not possible to state the relative effects of each independent variable, but the signs are easily interpreted.

Table 2. Healthcare utilization cost and claims for South Carolina Medicaid recipients, 1997–2002

	African American (*n*=3016)	White (*n*=1060)
Resource	**mean ± standard deviation**	**mean ± standard deviation**
Ambulatory		
Cost	$2077±$5008	$1887±$5088
Claims	20.2±34.1	18.9±31.4
Hospital		
Cost	$1383±$7909	$1174±$7787
Claims	2.0±4.4	1.6±3.7
Drugs		
Cost	$1620±$1987	$2170±$2083
Claims	27.0±20.9	33.6±24.4

DISCUSSION

Medicaid recipients prescribed fixed-dose combination amlodipine besylate/benazepril HCl had higher rates of compliance with antihypertensive therapy than did those prescribed free-combination DHP-CCB plus ACEI, independent of race. African American Medicaid recipients had lower compliance rates than did White patients, which may have contributed to higher costs and utilization associated with ambulatory and hospital services, as well as to lower medication costs and utilization. These results support findings of a previous study in a managed care population that was on average younger (mean age 53 years) and more evenly distributed by sex (50% female); the racial/ethnic composition of this managed care population was not specified. Patients prescribed fixed-dose combination amlodipine besylate/benazepril HCl had significantly higher rates of compliance and significantly lower average annual costs of cardiovascular-related care per patient than those prescribed a DHP-CCB plus ACEI as separate agents.[22] In general, compliance with medications is typically low among patients with chronic versus acute conditions and is inversely proportional to the frequency of dosing.[22]

Poor compliance with prescribed medication, as well as inadequate antihypertensive therapy, are potential contributing factors to low rates of blood pressure control. The Seventh Report of the Joint National Committee on Pre-

Table 3. Regression on the log of total cost of care

Dependent variable: log(total cost), mean = 7.9918, *N*=4076				
Variable	**Parameter**	**Standard Error**	***t***	***P* > t**
Intercept	7.0376	.0636	110.63	<.0001
Propensity score	−.2579	.0494	−5.22	<.0001
Year	−.0309	.0091	−3.41	.0007
MPR	.7118	.0482	14.76	<.0001
Group (fixed-dose = 1)	−.2437	.0453	−5.38	<.0001
Chronic disease score	.2052	.0056	36.72	<.0001
Race (White = 1)	−.0154	.0307	−.50	.6162
Sex (male = 1)	.0132	.0305	.43	.6660

Adjusted R^2=.3375, Model F = 297.47, P<.0001.

vention, Detection, Evaluation, and Treatment of High Blood Pressure suggests that most individuals with hypertension, particularly those at high risk, require two or more antihypertensive medications to achieve blood pressure goals.[3] For individuals who require a reduction of 20/10 mm Hg or more to reach goal, initiating therapy with two drugs separately or as a fixed-dose combination should be considered. Guidelines of the International Society on Hypertension in Blacks recommend combination therapy with an ACEI/CCB, ACEI/diuretic, angiotensin receptor blocker/diuretic, or β-blocker/diuretic in most patients who do not reach goal with monotherapy.[24] Combination therapy has the advantage of providing greater efficacy with lower doses of component agents along with the potential for a lower risk of adverse events.

In several studies, the combination of amlodipine plus benazepril was more effective for lowering blood pressure than either agent alone and was generally associated with comparable or fewer side effects than monotherapy.[25–29] Combination therapy with amlodipine besylate/benazepril HCl demonstrates greater efficacy with a lower incidence of side effects, such as edema associated with ACEIs, than amlodipine administered alone.[25,26,28] This is an important treatment consideration for African American patients, because ACEI-induced edema occurs two to four times more frequently in African American patients with hypertension than in other racial/ethnic groups.[3]

Furthermore, studies of patients whose blood pressure was inadequately controlled with benazepril or amlodipine monotherapy found that the combination resulted in significant blood pressure reductions, with good tolerability.[23–31] In a diverse patient population with inadequate blood pressure control or ankle edema with amlodipine monotherapy, 23% of whom were African American, 75% achieved a diastolic blood pressure goal of $<$90 mm Hg, and 85% experienced improvement in edema with fixed-dose amlodipine/benazepril.[31] Although there were differences in blood pressure reductions among the different racial groups studied, these differences were not statistically significant.

Another study in which blood pressure response was analyzed by race showed clinically significant reductions in all patient subgroups, including among African Americans who made up 25% of participants.[25] In patients with both hypertension and type 2 diabetes, 35.5% of whom were African American, treatment with fixed-dose combination amlodipine/benazepril resulted in a shorter time to blood pressure goal and a greater percentage of patients achieving blood pressure goal than did treatment with CCB monotherapy. When diuretics were added to CCB monotherapy, blood pressure control rates remained higher in patients who received fixed-dose amlodipine/benazepril.[32]

Among our sample overall, patients were considerably more likely to be prescribed the fixed-dose combination than the same drug classes as separate agents. Available data cannot explain the difference, but the magnitude of the difference (nearly five times) suggests that it is not a random event.

Some limitations of this study should be noted. Selection bias may exist since this study was retrospective and participants were not randomly assigned to treatment groups, although propensity scores were used to control for potential confounding factors present in the database. We could not confirm that prescribed antihypertensive drugs were actually taken, and clinical outcomes were not documented. Although using a Medicaid database has the advantage of providing complete information on a stable enrollee population, the South Carolina Medicaid population analyzed in this study was predominantly African American and female, which may limit the ability to generalize these results to the overall population.

African American Medicaid recipients had lower compliance rates than did White patients, which may have contributed to higher costs and utilization associated with ambulatory and hospital services

In conclusion, Medicaid recipients receiving fixed-dose combination amlodipine besylate/benazepril HCl were more compliant with antihypertensive therapy than were those receiving free-combination DHP-CCB plus ACEI, independent of race. The lower compliance rate of African American patients may have contributed to higher healthcare costs and utilization associated with ambulatory and hospital services. Efforts to enhance medication compliance tailored to African Americans may improve outcomes and reduce costs in this high-risk population.

ACKNOWLEDGMENTS

This study was supported by Novartis Pharmaceuticals Corporation through an unrestricted research grant to Dr Dickson. Data were originally presented at the National Medical Association Annual Convention and Scientific Assembly, July 23–28, 2005, New York, New York, USA.

REFERENCES

1. Mensah GA, Mokdad AH, Ford ES, Greenlund KJ, Croft JB. State of disparities in cardiovascular health in the United States. *Circulation*. 2005;111:1233–1241.
2. American Heart Association. *Heart Disease and Stroke Statistics—2006 Update*. Dallas; 2006.
3. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure:

the JNC 7 report. *JAMA*. 2003;289: 2560–2572.
4. US Department of Health and Human Services. *Healthy People 2010: Understanding and Improving Health*. 2nd edition. Washington: US Government Printing Office; 2000.
5. Gu Q, Paulose-Ram R, Dillon C, Burt V. Antihypertensive medication use among US adults with hypertension. *Circulation*. 2006; 113:213–221.
6. Hertz RP, Unger AN, Cornell JA, Saunders E. Racial disparities in hypertension prevalence, awareness, and management. *Arch Intern Med*. 2005;165:2098–2104.
7. Cheung BM, Ong KL, Man YB, Lam KS, Lau CP. Prevalence, awareness, treatment, and control of hypertension: United States National Health and Nutrition Examination Survey 2001–2002. *J Clin Hypertens*. 2006;8: 93–98.
8. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. *CMAJ*. 1999;160:31–37.
9. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. *CMAJ*. 1999;160:41–46.
10. Payne KA, Esmonde-White S. Observational studies of antihypertensive medication use and compliance: is drug choice a factor in treatment adherence? *Curr Hypertens Rep*. 2000;2:515–524.
11. Ogedegbe G, Harrison M, Robbins L, Mancuso CA, Allegrante JP. Barriers and facilitators of medication adherence in hypertensive African Americans: a qualitative study. *Ethn Dis*. 2004;14:3–12.
12. Hyman DJ, Pavlik VN. Poor hypertension control: let's stop blaming the patients. *Cleve Clin J Med*. 2002;69:793–799.
13. Oliveria SA, Lapuerta P, McCarthy BD, et al. Physician-related barriers to the effective management of uncontrolled hypertension. *Arch Intern Med*. 2002;162:413–420.
14. Elliott WJ. Optimizing medication adherence in older persons with hypertension. *Int Urol Nephrol*. 2003;35:557–562.
15. Elliott WJ. Compliance—and improving it—in hypertension. *Manag Care*. 2003; 12(8 Suppl Hypertension):56–61.
16. McCombs JS, Nichol MB, Newman CM, et al. The costs of interrupting antihypertensive drug therapy in a Medicaid population. *Med Care*. 1994;32:214–226.
17. Dickson M, Plauschinat CA. Antihypertensive therapy compliance and total cost of care in a Medicaid population: fixed-dose combination versus free combination treatment. [Abstract of meeting presentation. Journal article] *ASHP Summer Meeting*. 2005;62:P71E.
18. Sclar DA, Chin A, Skaer TL, Okamoto MP, Nakahiro RK, Gill MA. Effect of healthcare education in promoting prescription refill compliance among patients with hypertension. *Clin Ther*. 1991;13:489–495.
19. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and application. *J Clin Epidemiol*. 1997;50(1):105–116.
20. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to non-randomized control group. *Stat Med*. 1998;17:2265–2281.
21. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. *J Clin Epidemiol*. 1992;45: 197–203.
22. Taylor AA, Shoheiber O. Adherence to antihypertensive therapy with fixed-dose amlodipine besylate/benazepril HCl versus comparable component-based therapy. *Congest Heart Fail*. 2003;9:324–332.
23. Osterberg L, Blaschke T. Adherence to medication. *New Engl J Med*. 2005;353: 487–497.
24. Douglas JG, Bakris GL, Epstein M, Ferdinand KC, Ferrario C, Flack JM, et al. Management of high blood pressure in African Americans: consensus statement of the Hypertension in African Americans Working Group of the International Society on Hypertension in Blacks. *Arch Intern Med*. 2003;163:525–541.
25. Frishman WH, Ram CVS, McMahon FG, et al. Comparison of amlodipine and benazepril monotherapy to amlodipine plus benazepril in patients with systemic hypertension: a randomized, double-blind, placebo-controlled, parallel-group study. *J Clin Pharmacol*. 1995;35:1060–1066.
26. Kuschnir E, Acuna E, Sevilla D, et al. Treatment of patients with essential hypertension: amlodipine 5 mg/benazepril 20 mg compared with amlodipine 5 mg, benazepril 20 mg, and placebo. *Clin Ther*. 1996;18: 1213–1224.
27. Neutel JM, Smith DHG. Improving patient compliance: a major goal in the management of hypertension. *J Clin Hypertens*. 2003;5: 127–132.
28. Neutel JM, Smith DHG, Weber MA, Schofield L, Purkayastha D, Gatlin M. Efficacy of combination therapy for systolic blood pressure in patients with severe systolic hypertension: the Systolic Evaluation of Lotrel Efficacy and Comparative Therapies (SELECT) study. *J Clin Hypertens*. 2005;7:641–646.
29. Pool J, Kaihlanen P, Lewis G, et al. Once-daily treatment of patients with hypertension: a placebo-controlled study of amlodipine and benazepril vs amlodipine or benazepril alone. *J Hum Hypertens*. 2001;15:495–498.
30. Fogari R, Corea L, Cardoni O, et al. Combined therapy with benazepril and amlodipine in the treatment of hypertension inadequately controlled by an ACE inhibitor alone. *J Cardiovasc Pharmacol*. 1997;30:497–503.
31. Messerli FH, Weir MR, Neutel JM. Combination therapy of amlodipine/benazepril versus monotherapy of amlodipine in a practice-based setting. *Am J Hypertens*. 2002;15:550–556.
32. Bakris GL, Weir MR. Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) Investigators. Achieving goal blood pressure in patients with type 2 diabetes: conventional versus fixed-dose combination approaches. *J Clin Hypertens*. 2003;5:202–209.

AUTHOR CONTRIBUTIONS

Design concept of study: Dickson, Plauschinat
Acquisition of data: Dickson
Data analysis and interpretation: Dickson
Manuscript draft: Dickson, Plauschinat
Statistical expertise: Dickson
Acquisition of funding: Dickson, Plauschinat
Administrative, technical, or material assistance: Plauschinat
Supervision: Dickson