

# Antihypertensive Prescriptions for Newly Treated Patients Before and After the Main Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Results and Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Guidelines

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**Abstract**—Main results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial were published in December 2002. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, published in May 2003, recommended thiazide-type diuretics as initial pharmacological treatment alone or in combination with another drug in most patients with hypertension. To assess changes from before to after these publications, we compared antihypertensive medication prescriptions filled by patients who initiated pharmacological antihypertensive treatment in a large managed care organization during 3 time periods: (1) July 1, 2001, to June 30, 2002 (before these publications; n=1354); (2) July 1, 2003, to June 30, 2004 (to assess short-term changes; n=1542); and (3) July 1, 2004, to June 30, 2005 (to assess extended changes; n=1865). The percentage of patients initiating antihypertensive treatment with a thiazide-type diuretic increased from 30.6% to 39.4% ( $P<0.001$ ) between 2001–2002 and 2003–2004, and the increase was maintained at 36.5% in 2004–2005 ( $P<0.001$  compared with 2001–2002 and  $P=0.33$  compared with 2003–2004). Among patients without diabetes mellitus, renal disease, a history of myocardial infarction, or heart failure, the percentage initiating pharmacological antihypertensive treatment with a thiazide-type diuretic increased from 33.1% in 2001–2002 to 43.4% in 2003–2004 ( $P<0.001$ ) and remained increased (41.0%) in 2004–2005 ( $P<0.001$  and  $P=0.23$  compared with 2001–2002 and 2003–2004, respectively). Despite a sustained increase in the use of thiazide-type diuretics, this study indicates that an opportunity exists to increase adherence to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines. (*Hypertension*. 2009;53:617-623.)

**Key Words:** hypertension ■ antihypertensive agents ■ thiazide diuretics ■ clinical trials ■ epidemiology

In December 2002, the main results of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) were published; there was no difference in the primary outcome (fatal coronary heart disease and non-fatal myocardial infarction) or mortality between the randomized arms, but the incidence of heart failure was lower in the chlorthalidone group compared with the doxazosin, amlodipine, and lisinopril groups and the occurrence of stroke and combined cardiovascular disease outcomes were lower in the chlorthalidone group compared with the doxazosin and lisinopril groups.<sup>1,2</sup> Based on ALLHAT and results from other

outcome trials in hypertension since the 1960s, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) in 2003 recommended that a thiazide-type diuretic be used alone or in combination with another agent as initial pharmacological antihypertensive therapy in most patients, unless a compelling indication for use of an alternate medication was present.<sup>3</sup>

Results from randomized, controlled trials form the foundation of evidence used in the development of clinical practice guidelines. These guidelines are thought to have

Received July 21, 2008; first decision August 4, 2008; revision accepted January 15, 2009.

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*Hypertension* is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.108.120154

substantial influence on patterns of medication prescribing. However, limited change may occur in physician practice and prescription patterns after the publication of clinical trial findings. In this context, a concerted multifaceted effort was made to disseminate the results of ALLHAT. This dissemination effort was the first application of a National Heart, Lung, and Blood Institute policy requiring a detailed dissemination plan for trials with potential immediate public health applicability.

The current analyses were conducted to contrast initial antihypertensive drug therapy prescriptions filled by patients within a large managed care organization before and after the publication of the major outcomes of ALLHAT in December 2002 and JNC 7 guidelines in May 2003.

## Methods

### Study Population

The patients identified for this study were drawn from a large managed care organization, located in the southeastern United States, which offers healthcare benefits to nearly 200 000 persons enrolled in commercial or Medicare risk plans. The mean age of all of the patients taking antihypertensive medications in this organization was 63 years, and 55% were women. This is similar to all US adults taking antihypertensive medications (mean age: 61 years and 52% women), as estimated using data from the 2003–2004 National Health and Nutrition Examination Survey.<sup>4</sup> This study included 3 cohorts of patients initiating antihypertensive treatment between the following dates: (1) July 1, 2001, and June 30, 2002, to describe prescriptions filled before the ALLHAT and JNC 7 publications; (2) July 1, 2003, and June 30, 2004, to assess short-term changes in prescription patterns after release of these publications; and (3) July 1, 2004, and June 30, 2005, to assess the extended changes.

The study population was limited to patients  $\geq 21$  years of age who remained continuously enrolled in the managed care organization for  $\geq 3$  years with no antihypertensive prescriptions filled before each study period and with  $\geq 1$  antihypertensive medication prescription filled during each study period. To increase the likelihood that patients were being prescribed medication to lower their blood pressure, we limited the sample to patients with  $\geq 1$  clinic visit with a primary diagnosis of hypertension (International Classification of Diseases, 9th Revision, [ICD9] code 401.X). Medications listed as oral antihypertensive agents in JNC 7 were used to identify patients initiating a pharmacological antihypertensive regimen. For the current analyses, drugs were grouped into 6 classes (diuretics,  $\beta$ -blockers, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers, and others [eg,  $\alpha$ - $\beta$ -blocker, adrenergic peripheral, and adrenergic central]) with further subcategorization performed for diuretics (thiazide-type, loop, and potassium-sparing). To assess trends in renin angiotensin system blockers filled, ACE inhibitors and angiotensin receptor blockers were also combined.

### Data Collection

The managed care organization's data warehouse system was the source of the computerized patient record data. Patient data included age, gender, and enrollment dates. Outpatient encounter information included the dates and code(s) for visits that included a primary diagnosis of hypertension. Pharmacy data included antihypertensive prescription fill date and generic and brand name. Data on selected comorbid conditions were extracted from administrative databases using primary and secondary diagnosis and procedure codes (ie, diabetes mellitus [ICD9 250.XX], myocardial infarction [ICD9 codes 410.XX and 412.XX], heart failure [ICD9 428.XX], and renal disease [ICD9 580.XX–589.XX, 753.1, 593.XX, 403.XX, and 404.XX]). Race information was collected from patients' medical charts.

All aspects of the study were approved by the institutional review boards of Tulane University, Ochsner Clinic Foundation, and the privacy committee of the managed care organization. All of the patient identification information was collected and maintained according to Health Insurance Portability and Accountability Act regulations and the managed care organization's privacy rules.

### Statistical Methods

Characteristics of patients initiating antihypertensive medication were calculated for the 3 study periods (2001–2002, 2003–2004, and 2004–2005), separately, as means for continuous variables and percentages for categorical variables. The percentage of patients initiating antihypertensive therapy with  $\geq 2$  drug classes was calculated for each time period. The distribution of each drug class filled was calculated as a percentage of all of the patients initiating antihypertensive medication for each time period. Distributions were calculated for the overall population, for persons with and without diabetes mellitus, for black and white patients, and limiting the population to patients initiating pharmacological antihypertensive therapy with a single drug class. Next, the percentage of patients who filled a thiazide-type diuretic as part of their initial pharmacological antihypertensive therapy was calculated for each time period after limiting the study sample to patients without commonly accepted reasons for receipt of a specific class of antihypertensive medication (ie, those who were not diagnosed with diabetes mellitus, myocardial infarction, heart failure, or renal disease). The statistical significances of changes in each drug class filled from 2001–2002 to 2003–2004 and 2004–2005, separately, were calculated using  $\chi^2$  tests. In addition,  $\chi^2$  tests were used to calculate the statistical significance of changes in each drug class between 2003–2004 and 2004–2005. Finally, the 2003–2004 and 2004–2005 data were pooled and the multivariable-adjusted prevalence ratios of being prescribed each antihypertensive drug class, as well as initiating antihypertensive treatment with  $\geq 2$  drug classes, associated with demographic characteristics and a history of myocardial infarction and diabetes mellitus, were calculated. Prevalence ratios were calculated using log-binomial regression models that included all of the independent variables simultaneously.<sup>5</sup> Prevalence ratios for 2003–2004 and 2004–2005 analyzed separately were similar (data not shown). Analyses were performed using SAS 9.1 (SAS Institute, Inc) and Stata 9.0 (Stata Corp).

### Results

The gender and race distributions of patients initiating antihypertensive medications were similar across the 3 study periods. On average, patients initiating antihypertensive medication were 4.5 years older in the 2004–2005 study period compared with those who initiated treatment in 2001–2002 (Table). A history of comorbid conditions, including myocardial infarction, congestive heart failure, renal disease, and diabetes mellitus, was more common among patients initiating therapy in the latter periods. Overall, in 2001–2002, 24% of patients initiated pharmacological antihypertensive treatment with  $\geq 2$  drug classes, including fixed-dose combination drugs. This percentage increased to 31% in 2003–2004 and stayed at 31% in 2004–2005 ( $P < 0.0001$  comparing 2003–2004 and 2004–2005, separately, with 2001–2002). The use of fixed-dose combination medications, among patients initiating pharmacological antihypertensive treatment, increased from 19% to 25% from 2001–2002 to 2003–2004 ( $P < 0.001$ ) and stayed increased at 23% in 2004–2005 ( $P < 0.01$  compared with 2001–2002).

Among all of the patients initiating pharmacological antihypertensive treatment, including those initiating therapy with a single drug or with combination therapy, the percentage of patients initiating treatment with a thiazide-type

**Table. Characteristics of Participants Initiating Antihypertensive Medication Before (July 1, 2001, to June 30, 2002) and After (July 1, 2003, to June 30, 2004, and July 1, 2004, to June 30, 2005) the Publication of the Main ALLHAT Study Findings and JNC 7 Guidelines**

Variable	July 1, 2001, to June 30, 2002 (N=1354)	July 1, 2003, to June 30, 2004 (N=1542)	July 1, 2004, to June 30, 2005 (N=1859)
Age, mean (SD), y	58.2 (14.4)	61.3 (14.8)‡	62.7 (14.8)‡
Women, %	54.7	54.5	56.9
Race*			
White, %	68.9	67.7	70.9
Black, %	27.7	29.4	27.1
Other, %	3.4	3.0	2.0
Baseline comorbid conditions			
Myocardial infarction, %	1.2	2.3†	2.4†
Congestive heart failure, %	1.7	3.8‡	6.3‡§
Renal disease, %	0.5	2.2‡	5.9‡§
Diabetes mellitus, %	12.8	15.7†	20.0‡§

Data are from References 1 and 3.

\*Data were not available on race for 246 participants (18.2%) in 2001–2002, 261 participants (16.9%) in 2003–2004, and 383 participants (20.6%) in 2004–2005.

† $P < 0.05$ ; ‡ $P < 0.001$  comparing means and percentages in 2003–2004 and 2004–2005 with 2001–2002.

§ $P < 0.001$  comparing means and percentages in 2004–2005 with 2003–2004.

diuretic increased from 30.6% to 39.4% ( $P < 0.001$ ) between 2001–2002 and 2003–2004, and the increase was maintained in 2004–2005 (36.5%;  $P < 0.001$  compared with 2001–2002 and  $P = 0.33$  compared with 2003–2004, respectively; Figure 1, left). Inclusion of  $\beta$ -blockers in patients' initial antihypertensive medication fills did not change across the time periods, and calcium channel blocker fill rates decreased in 2003–2004 but returned to the 2001–2002 levels in 2004–2005. In 2001–2002 and 2003–2004, a similar percentage of patients filled a prescription for an ACE inhibitor with a decline occurring by 2004–2005. In contrast, compared with the 2001–2002 time period, a higher percentage of patients initiating treatment in 2003–2004 and 2004–2005 filled a prescription for an angiotensin receptor blocker. Use of renin angiotensin system blockers (ie, ACE inhibitors or angiotensin receptor blockers) did not change over the 3 periods. Patterns were similar for each drug class among the subset of patients initiating pharmacological antihypertensive therapy with a single drug class (Figure 1, right).

The time trends for filled antihypertensive medications observed for the overall population were similar among patients without diabetes mellitus and whites (Figure 2). The percentage of patients with diabetes mellitus in 2001–2002 initiating antihypertensive drug therapy with a  $\beta$ -blocker was lower than for their counterparts without diabetes mellitus. However, an increase was noted in the percentage of patients with diabetes mellitus initiating antihypertensive drug ther-

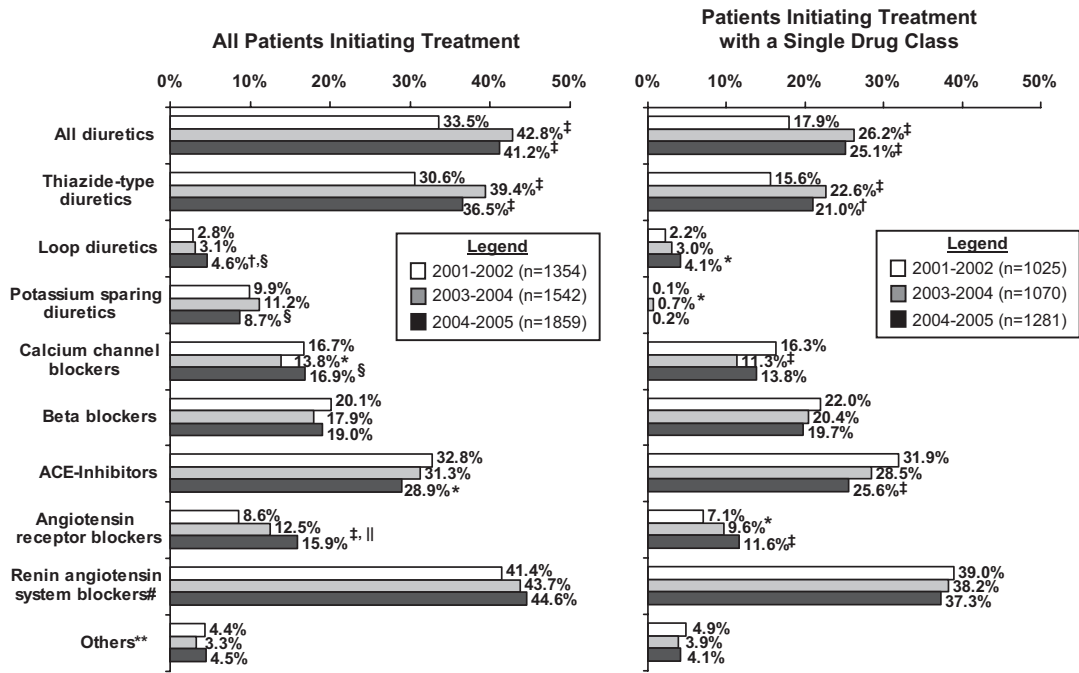
apy with a  $\beta$ -blocker such that  $\beta$ -blocker use was similar for patients with and without diabetes mellitus in 2004–2005. A decline in the percentage of patients with diabetes mellitus filling an ACE inhibitor or renin-angiotensin system blockers as part of their initial treatment regimen occurred between 2001–2002 and 2004–2005. Although the percentage of black patients filling a thiazide-type diuretic increased significantly between 2001–2002 and 2003–2004, this increase was not maintained through 2004–2005. However, in each time period studied, the percentage of black patients who filled their initial antihypertensive prescription with a thiazide-type diuretic was higher than for whites. Also, whereas there was no increase in ACE inhibitor use by black patients over time, the use of angiotensin receptor blockers and renin-angiotensin system blockers increased in black patients. In each time period, <50% of patients initiating antihypertensive treatment without a commonly cited reason for receipt of a specific class of antihypertensive medication filled a thiazide-type diuretic. Specifically, the percentage of patients without diabetes mellitus, myocardial infarction, heart failure, or renal disease initiating treatment with a thiazide-type diuretic increased from 33.1% to 43.4% from 2001–2002 ( $P < 0.001$ ) through 2003–2004 and was 41.0% in 2004–2005 ( $P < 0.001$  and  $P = 0.23$  compared with 2001–2002 and 2003–2004, respectively).

In 2003–2005, the periods after publication of ALLHAT and JNC 7, patients  $\geq 65$  years of age were more likely than younger patients to initiate antihypertensive treatment with a  $\beta$ -blocker or calcium channel blocker (Figure 3). Women were more likely than men to initiate treatment with a thiazide-type diuretic. Black patients were more likely than white patients to have a thiazide-type diuretic and calcium channel blocker included in their initial treatment. Patients with a history of myocardial infarction were more likely to fill a prescription for a  $\beta$ -blocker. Patients with diabetes mellitus were more likely to fill a prescription for an ACE inhibitor as part of their first-line antihypertensive drug regimens.

In a multivariate regression model including age, gender, race, and the presence of diabetes mellitus and myocardial infarction, patients who were  $\geq 65$  versus  $< 65$  years of age were 1.12 (95% CI: 0.99 to 1.26) times more likely to initiate antihypertensive therapy with  $\geq 2$  drug classes. In addition, after multivariate adjustment, women and black patients were 1.17 (95% CI: 1.03 to 1.32) and 1.45 (95% CI: 1.26 to 1.68) times more likely, respectively, to initiate antihypertensive therapy with  $\geq 2$  drug classes than men and white patients, respectively. In contrast, patients with, compared to without, diabetes mellitus were less likely (prevalence ratio: 0.80; 95% CI: 0.67 to 0.95) to initiate antihypertensive therapy with  $\geq 2$  drug classes. Having a history of myocardial infarction was not associated with initiating antihypertensive therapy with  $\geq 2$  drug classes (prevalence ratio: 1.17; 95% CI: 0.78 to 1.74).

## Discussion

In this study, a higher percentage of patients initiated pharmacological antihypertensive therapy with a thiazide-type diuretic in 2003–2004 compared with 2001–2002. This time interval represents periods before and after the publication of the main results of ALLHAT and JNC 7 guidelines in December 2002



\* P<0.05; † P<0.01; ‡ P<0.001 comparing percentages in 2003-2004 and 2004-2005 to 2001-2002.  
 § P<0.05; || P<0.01; ¶ P<0.001 comparing percentages in 2004-2005 to 2003-2004.  
 # Includes angiotensin converting enzyme inhibitors and angiotensin receptor blockers  
 \*\*Others includes alpha blockers, alpha-beta blockers, adrenergic peripherals and adrenergic centrals.

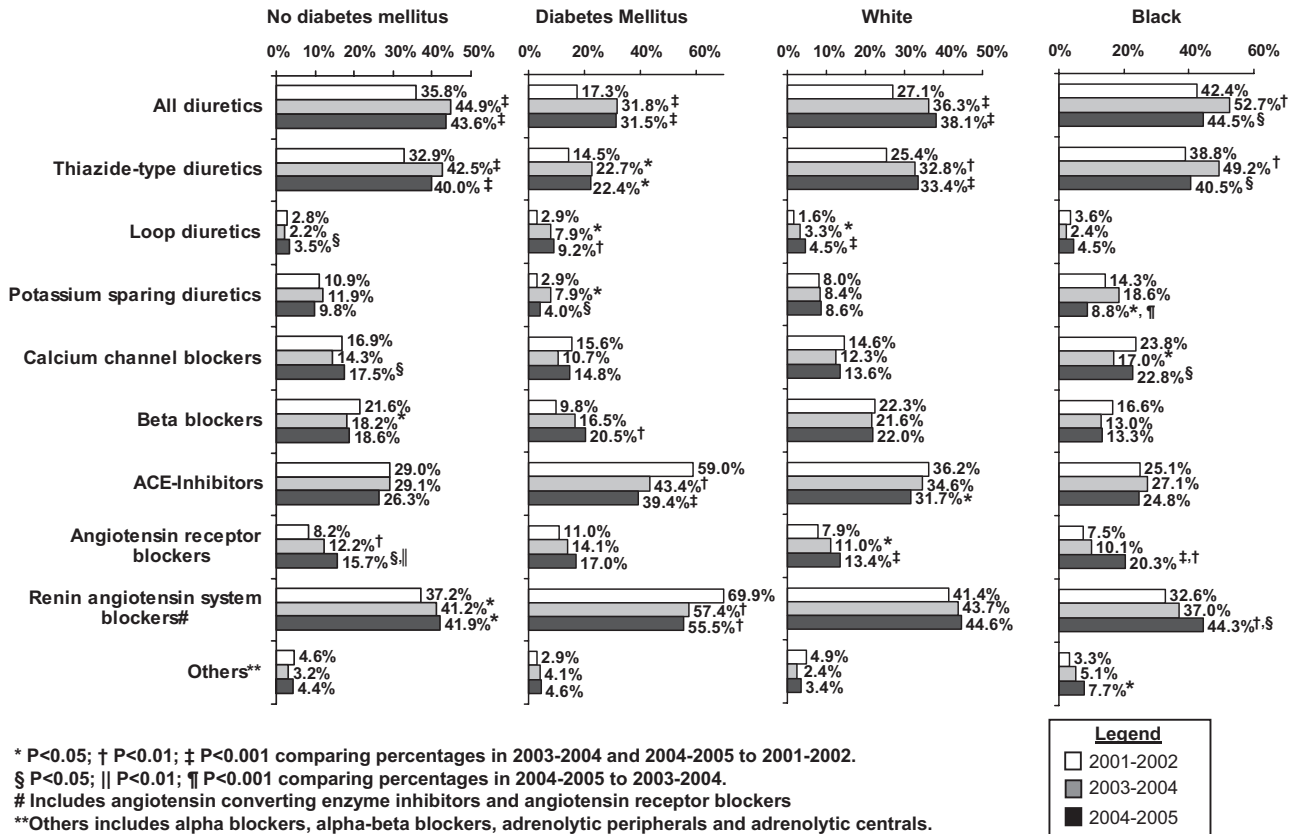
**Figure 1.** Percentage of patients' initial antihypertensive medications filled by drug class and calendar time for all of the patients and those initiating treatment with a single drug class.

and May 2003, respectively. Increased rates of thiazide-type diuretics filled as a first-line antihypertensive medication persisted through 2004–2005 but did not increase further.

In JNC 7, ACE inhibitors and angiotensin receptor blockers are recommended for patients with kidney disease and heart failure. Although JNC 7 did not consider diabetes mellitus a compelling indication for antihypertensive treatment other than a thiazide-type diuretic, the American Diabetes Association guidelines recommended that patients with diabetes mellitus receive an ACE inhibitor or angiotensin receptor blocker as part of their initial regimen. In the current study, we observed a significant decline in the percentage of patients with diabetes mellitus who filled a renin-angiotensin system blocker as part of their initial antihypertensive drug therapy. A previous study of patients with hypertension and diabetes mellitus in Canada initiating antihypertensive therapy reported a marked increase in ACE inhibitors as the first drug class filled from 1995 to 2000 followed by a small decrease in 2001. However, more recent data have not been published. The decrease in ACE inhibitors as the initial drug class filled by patients with diabetes mellitus in the current study may be because of reliance on ICD9 codes for defining diabetes mellitus. Also, the use of  $\beta$ -blockers increased significantly among patients with diabetes mellitus in the current study. Although not considered renin inhibitors,  $\beta$ -blockers lower renin levels. Finally, the decline in the renin-angiotensin system blockers among patients with diabetes mellitus may be attributed to the benefits of chlorthalidone over lisinopril among patients with diabetes mellitus in ALLHAT. Despite the decline in renin-angiotensin blockers

filled in the time period after publication of ALLHAT and JNC 7, patients with diabetes mellitus were 50% and 22% more likely than those without diabetes mellitus to have their initial therapy include an ACE inhibitor or angiotensin receptor blocker, respectively.

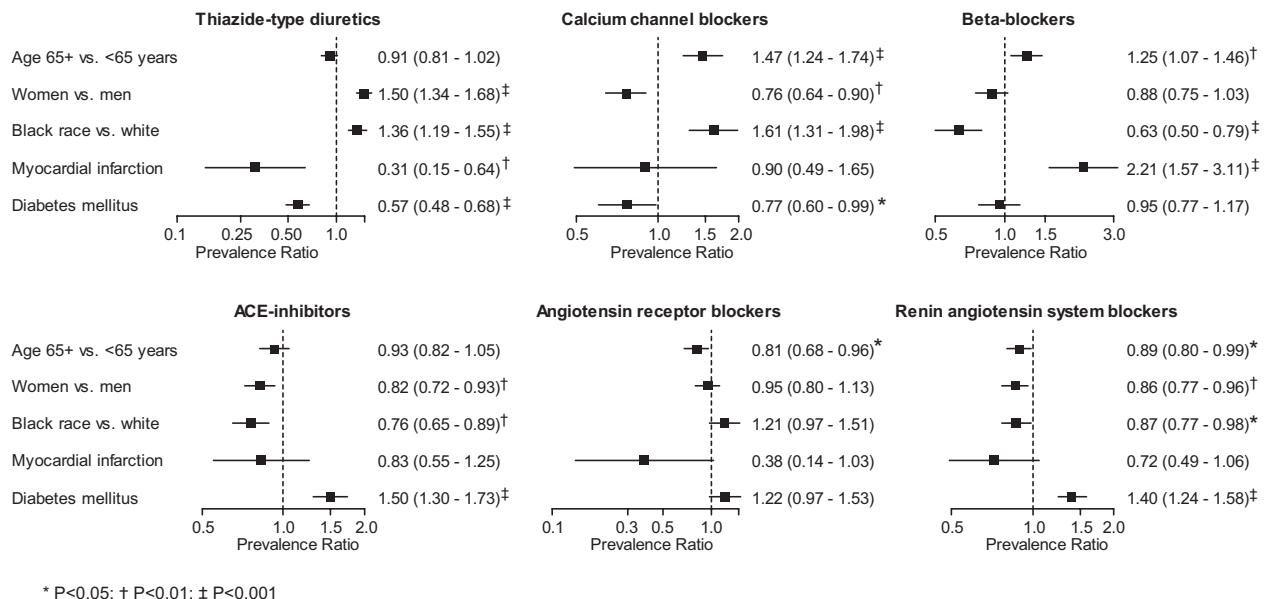
Medication prescribing, particularly for a disease as prevalent as hypertension, is a complex practice for which evidence-based recommendations represent only one of many influencing factors.<sup>6,7</sup> Other factors may include potential drug interactions, drug marketing, patient or provider bias or preferences, formularies, and drug price.<sup>8,9</sup> These factors may have limited the impact of ALLHAT on prescription fill patterns. Although many clinicians and researchers supported the ALLHAT recommendations and readily adopted the JNC 7 guidelines, others questioned the results of ALLHAT and the JNC 7 guidelines<sup>10–12</sup> and likely did not use the guidelines in clinical decision-making. Also, new classes of antihypertensive medications, most notably, angiotensin receptor blockers, were not included as a treatment arm in ALLHAT. Although a recent trial showed the effectiveness of the angiotensin receptor blocker losartan, compared with a  $\beta$ -blocker and “usual care,” on cardiovascular mortality, stroke, and myocardial infarction, no drugs in this class have been compared directly with thiazide-type diuretics.<sup>13</sup> In addition to ALLHAT and JNC 7, other clinical trials were published during the time period under study. Results from the African-American Study of Kidney Diseases and Hypertension Study group were published in November 2002 and demonstrated the benefits of ACE inhibitors versus  $\beta$ -blockers and calcium channel blockers on slowing the decline in glomerular filtration rate among blacks with



**Figure 2.** Percentage of participants who filled each antihypertensive medication class by diabetes mellitus status, race, and calendar time.

chronic kidney disease.<sup>14</sup> However, there was no evidence of a benefit for ACE inhibitors, compared with thiazide-type diuretics, among patients with diabetes mellitus or chronic kidney disease in ALLHAT.<sup>15,16</sup> Also, the Controlled Onset Verapamil Investigation of Cardiovascular End Points Trial was published in April 2003.<sup>17</sup> However, the results of this

trial are consistent with the findings from ALLHAT; no difference was present in cardiovascular outcomes or all-cause mortality, and the incidence of heart failure was higher for patients randomly assigned to verapamil versus the choice of atenolol or hydrochlorothiazide over 3 years average follow up in this trial.



**Figure 3.** Multivariable adjusted prevalence ratios (95% CIs) of filling each antihypertensive medication class as part of an initial treatment regimen during the 2003–2005 study period.

In the decades before the publication of the main ALLHAT findings, the use of diuretics declined markedly. Using national prescription data, Manolio et al<sup>18</sup> reported a 52% decline in diuretics prescribed from 1982 through 1993. Furthermore, the use of diuretics declined among a cohort of older adults between 1989–1990 and 1998–1999.<sup>19</sup> Trends through 2002 (ie, still before the ALLHAT publication) indicate that a low percentage of patients with hypertension were prescribed diuretics.<sup>20</sup> An analysis of the National Disease and Therapeutic Index, nationally representative data reported by office-based physicians in the United States on patient encounters, including drug prescription information, found an increase in thiazide-type diuretic use between 1998 and 2000.<sup>21</sup> Although data for the current study were not available before 2001, no change in the percentage of patients who initiated antihypertensive therapy with a thiazide-type diuretic was present between July 1, 2001, and December 31, 2001 (31.7%), and January 1, 2002, and June 30, 2002 (29.3%).

At least 3 previous studies have evaluated changes in antihypertensive prescription patterns from before to after publication of the main ALLHAT findings.<sup>22–24</sup> Stafford et al<sup>22</sup> reported 26% and 22% decreases in  $\alpha$ -blocker orders and dispensed prescriptions, respectively, after the early termination of that randomization arm in ALLHAT in 2000. Two studies reported changes in antihypertensive prescription patterns after the publication of the main outcomes of ALLHAT in December 2002.<sup>23,24</sup> Despite different study populations and methodologies, similar trends were reported. After excluding patients who had filled an antihypertensive medication in the previous year, the percentage of patients enrolled in the Kaiser Permanente of Southern California managed care organization filling thiazide-type diuretics increased from 16.7% to 21.4% from the year before to the one after publication of major outcomes in ALLHAT.<sup>23</sup> In addition, Player et al<sup>24</sup> reported an increase in thiazide-type diuretic prescriptions from 29.4% to 39.1% among a network of outpatient offices in the same years. Data from the 2005–2006 National Health and Nutrition Examination Survey indicate that 65 million US adults have hypertension, of whom 44 million report taking antihypertensive treatment.<sup>25</sup> As such, the higher rates of thiazide-type diuretics prescribed after ALLHAT may, over time, translate into a change in treatment for several million US adults initiating antihypertensive therapy.

This study's results need to be interpreted within the context of its limitations. Most importantly, it focused on a patient population with health insurance in a large managed care organization. Although this may limit the study's generalizability, patients on antihypertensive treatment in the managed care organization were similar to US adults on treatment with respect to age and gender. Also, this population provided the opportunity to use several unique data sources and to minimize the confounding effects of health insurance on ability to fill prescriptions. Patients in the managed care organization initiating antihypertensive treatment were older in 2004–2005 than the earlier time periods. This may have resulted from administrative changes in enrollment plans offered by the managed care organization. Patients  $\geq 65$  years of age were nonsignificantly less likely to

receive a thiazide-type diuretic as part of their initial antihypertensive regimen. Therefore, the older population in the last time period may explain the absence of an increase in thiazide diuretic use from 2003–2004 to 2004–2005. Another limitation is that the pharmacy database only maintained a listing of prescriptions patients filled, and we were unable to capture medications prescribed but not filled by patients. In addition, patients who filled their prescriptions with third-party insurance were not captured, and the current analysis was limited to patients who used the managed care organization's drug plan. The study also exhibits several strengths. The databases provided a large sample size and clinically relevant information, such as comorbid diagnoses. We were able to limit the population to patients who had not filled an antihypertensive medication in the previous 2 years. Also, the use of administrative databases permitted us to analyze patients with an outpatient primary diagnosis of hypertension. These criteria provide confidence that the patients studied were initiating a pharmacological regimen for the treatment of hypertension. In addition, the data sources used permitted us to assess treatment patterns for patients with and without diabetes mellitus and with no compelling indications for receiving an antihypertensive agent other than a thiazide-type diuretic.

### Perspectives

The percentage of patients initiating an antihypertensive medication regimen that included a thiazide-type diuretic increased from the year before to after the publication of the main outcomes of ALLHAT and was maintained in the second year following these publications. Although this is impressive, less than half of the patients initiated pharmacological antihypertensive therapy with a thiazide-type diuretic as part of their regimen. This held true for patients without commonly accepted indications for receiving an antihypertensive other than a thiazide-type diuretic. This finding highlights a substantial disconnect between the JNC 7 clinical guidelines and physician practice. Dedicated efforts are needed to understand the reasons that clinical practice guidelines are not more widely followed and to implement interventions to enhance their impact.

### Acknowledgment

We thank Phyllis Nitzkin for her assistance with the data management.

### Sources of Funding

The ALLHAT Study was supported by a contract with the National Heart, Lung, and Blood Institute. The ALLHAT investigators acknowledge contributions of study medications supplied by Pfizer, Inc (amlodipine and doxazosin), AstraZeneca (atenolol and lisinopril), and Bristol-Myers Squibb (pravastatin), as well as financial support provided by Pfizer, Inc.

### Disclosures

W.C.C. has grants and contracts with Abbott Laboratories; consults for Bristol-Myers Squibb, Calpis, Gilead Colorado, Johnson & Johnson, King, Myogen, Novartis, Pfizer, Roche, Sankyo, Sanofi Aventis, Sciele, and Takeda; and has received honoraria from Astra-Zeneca, Boehringer Ingelheim, Forest Pharmaceuticals, King, Novartis, and Sankyo. The remaining authors report no conflicts.

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