Blood Pressure Outcomes in Patients Receiving Angiotensin II Receptor Blockers in Primary Care: A Comparative Effectiveness Analysis From Electronic Medical Record Data

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The authors examined the comparative effectiveness of 4 angiotensin receptor blockers (ARBs) in patients with hypertension using a large electronic medical record database. Analysis of covariance and logistic multivariate regression models were used to estimate the blood pressure (BP) outcomes of 73,012 patients during 13 months of treatment with olmesartan, losartan, valsartan, and irbesartan. Results were adjusted by baseline BP, starting dose, year, age, sex, race, body mass index, comorbid conditions, and concomitant medications of patients. All ARBs led to sustained reductions in BP, but with significant differences in the magnitude of BP reduction. Raw mean systolic BP/diastolic BP reductions with losartan, valsartan, irbesartan, and olmesartan were 9.3/4.9 mm Hg, 10.4/5.6 mm Hg, 10.1/5.3 mm Hg, and 12.4/6.8 mm Hg, respectively. Adjusting for all covariates, the overall BP reductions with olmesartan were 1.88/0.86 mm Hg, 1.21/0.52 mm Hg, and 0.89/0.51 mm Hg greater than for losartan, valsartan, and irbesartan, respectively, and mean differences were higher for monotherapy: 2.43/1.16 mm Hg; 2.18/0.93 mm Hg; 1.44/0.91 mm Hg, respectively (all P values $<.0001$). Adjusted odds ratios of the JNC 7 goal attainment for losartan, valsartan, and irbesartan compared with olmesartan were 0.76, 0.86, and 0.91 ($P<.05$). Differences were also found in subpopulations: African Americans, diabetics, and obese/overweight patients but not all of these reached statistical significance. A broad choice of ARBs may be required to get patients to treatment goals. *J Clin Hypertens (Greenwich).* 2011;13:801–812. ©2011 Wiley Periodicals, Inc.

Clinical management of systemic hypertension continues to be an important primary focus to reduce the risk of cardiovascular and renal disease in patients. Worldwide prevalence of hypertension approaches 1 billion patients, with nearly 74 million in the United States, making it one of the most prevalent clinical disorders.[1] Untreated hypertension is associated with premature mortality and morbidity, including fatal and nonfatal stroke,[2] myocardial infarction,[3,4] coronary heart disease,[5] renal damage,[6,7] and vascular death.[8] The graduated link between blood pressure (BP) control and reduction in cardiovascular morbidity and mortality has been clearly established and accepted in clinical practice.[9–12] The National Health and Nutrition Examination Survey (NHANES) suggests that the number of patients with hypertension has increased by approximately 10 million individuals from 1999 to 2006, an increase of 15%.[13–15] The prevalence of hypertension among non-Hispanic white men increased from 25.6% to 29.9% between 1988 and 2006. During that same period, the prevalence of hypertension among non-Hispanic African American men increased from 37.5% to 41.8%.[16]

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Blood pressure goals in the treatment of hypertension have been established by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7), which recommends that elevated BP be reduced to <140/90 mm Hg (or <130/80 mm Hg for patients with diabetes or chronic kidney disease [CKD]).[17] Healthy People 2000 (now extended to 2010) sets a goal of 50% BP control rate.[17] Research findings suggest that just more than one fourth of patients (28%) have achieved this attainment threshold, and that most patients with hypertension will require 2 antihypertensive medications to achieve target BP, exemplifying a continuing need to evaluate the effectiveness of current therapies for hypertension.[18,19] However, rates of goal attainment may be increasing. Age-adjusted NHANES data from 2007 to 2008 show that 50% of patients with hypertension achieved BP control of <140/90 mm Hg, which is an improvement over the 35% reported in the 2003 to 2004 survey.[15]

Angiotensin II receptor blockers (ARBs) are one of the relatively newer classes of antihypertensive agents. They have been shown to be effective in reducing BP and cardiovascular disease and have a good tolerability profile. The clinical trial literature on the effectiveness of ARBs is robust, but largely tends to be based on shorter-term data. Comparative efficacy of ARBs in clinical trials has also been reported, but not all commonly used ARBs are compared in most studies.

Recently, a decision analytic economic evaluation of the 4 most widely prescribed ARBs was reported using retrospective medical chart review;[20] however, BP readings were obtained from a limited number of charts and current literature remains sparse on the effectiveness of the ARBs in real-world treatment settings.

The primary purpose of this study was to compare the effectiveness of ARBs by evaluating BP response rates in patients with hypertension in their usual ambulatory clinical care settings, with data drawn from electronic medical records (EMRs). According to IMS national audit data (IMS Health Incorporated, Norwalk, CT), valsartan (VAL), olmesartan medoxamil (OM), losartan potassium (LOS), and irbesartan (IRB) are the most frequently prescribed ARBs in the United States, and their use as monotherapy and as combination therapy with hydrochlorothiazide (HCTZ) is widely accepted. In addition, considerable evidence exists that certain subpopulations of patients have greater difficulty with BP reduction and goal attainment: these include African Americans, patients with diabetes, and overweight and obese patients. Therefore, we assessed the clinical effectiveness of ARB therapies in these important special subpopulations as well.

This study offers a large analysis of the comparative effectiveness of ARBs in the setting of clinical practice. Examination of the effectiveness of the treatment modalities on the systolic BP (SBP), diastolic BP (DBP), and overall BP goal attainment is derived using substantive physician-recorded information extracted from EMR data from ambulatory care settings across the United States. This examination of BP outcomes in real-life care offers the opportunity to not only assess the effectiveness of ARB therapies, with and without other concomitant medications, it also can provide a real-world context for the relevance of clinical trial findings. In addition, it provides an analysis of BP goal attainment in traditionally hard-to-treat populations.

METHODS

Data Source

The data source used for the study was the GE Centricity EMR Database (GE Healthcare, Waukesha, WI). As of December 2008, the GE Centricity EMR database contained ambulatory electronic health record data for more than 11 million patients from more than 6000 participating physicians, of whom approximately 63% were primary care physicians. These EMR data are certified Health Insurance Portability and Accountability Act–compliant and reviewed for clinical accuracy in a rigorous quality-controlled process. Data are entered at the point of care by the clinical staff. Patient records in the database are de-identified and the database constitutes the secondary data source for analyses.

The database contains longitudinal clinical patient data including, but not limited to, demographic information (age, sex, race, geographic location, insurance, and type of payment) and substantive clinical information (diagnosis, vital signs, body mass index [BMI], medications, prescriptions, laboratory test orders, and results). In addition, the medical charts detail prescribing patterns and longitudinal observations for office-based BP readings.

Study Population

Patients were required to meet the following eligibility criteria: age 18 years or older, diagnosis for hypertension (*International Statistical Classification of Diseases and Related Health Problems–Ninth Revision* [*ICD-9*] codes: 401.xx–404.xx) verified with actual SBP and DBP $\geq$130/80 mm Hg at the time of initiation of therapy with ARB, and at least one prescription for OM, VAL, LOS, or IRB alone or in combination with HCTZ. The study eligibility period was from February 1997 through November 2007. The index date was defined as the date of initiation of ARB therapy by the physician at any point during this time. Clinical activity in the EMR for at least 13 months prior to the index date (with BP readings available but no ARBs prescribed) and at least 13 months post-index date was required for inclusion in the analysis sample. Thus, the study analysis period was from January 1996 through December 2008.

Diabetic status for each patient was determined by *ICD-9* code 250 (including 250.x), and the use of antidiabetic medications, diagnosis dates, and prescription dates were compared with the index date, and a variable was created that flagged patients at index date as to their diabetes status. A CKD flag variable was created for each patient based on *ICD-9* code 585 and onset date in relation to index date. Since the EMR data contained data on height and weight of patients, BMI was calculated. Using World Health Organization (WHO) criteria, patients were classified as obese (BMI $\geq$30), overweight (BMI $\geq$25 to $<$30), or normal or underweight (BMI $<$25).

Outcome Measures

The primary outcomes for this study were changes in SBP and DBP from baseline and JNC 7 BP goal attainment rates. The JNC 7 BP goal attainment was defined as $<$140/90 mm Hg for the general population of patients with hypertension and $<$130/80 mm Hg for patients with hypertension who had diabetes or CKD.

Secondary analyses included evaluating the same predefined measures in 4 important subpopulations of interest: African Americans, patients with diabetes, patients with BMI indicative of being obese ($\geq$30), and patients with BMI indicative of being overweight (25 to $<$30). (Patients with CKD were initially included as a subgroup but the patient numbers were too small for the results to be meaningful.)

Statistical Methods

The longitudinal BP records of all eligible patients were included in the analysis. Each day's BP records

were averaged to obtain the daily average BP. The baseline BP was the value at index date, or, when missing, at most recent date within −30 to +1 of index date. Postbaseline BPs were obtained via daily records following the 5-day period after initiating ARBs, ie, from day 6 to day 395. Data from day 1 to day 5 were excluded, as the goal was to measure stable BP after initiation of ARBs.

The availability of daily-average BP varied greatly from patient to patient, with some patient charts containing several BP readings per month while others had ≤1 reading. Therefore, to smooth out differences in frequency of office-based BP measurement, we calculated average BP during larger segments of time. Thus, for the analyses, day 6 to day 395 were divided into 5 equal segments or "quarters" of 78 days each. Mean SBP and DBP during each of the segments were calculated. These quarterly mean BPs were summarized by 8 cohorts defined by the index ARB: OM, VAL, LOS, IRB, OM+HCTZ, VAL+HCTZ, LOS+HCTZ, or IRB+HCTZ. When the quarterly mean SBP and DBP were plotted for the 4 ARB cohorts and separately for the 4 ARB+HCTZ cohorts, certain patterns emerged. Based on these patterns, the BP data and treatment cohorts were consolidated and multivariate regressions were performed as noted below.

For multivariate regressions, the 5 quarterly means were averaged to become the overall postbaseline/treatment-effect BP levels, representing the mean postbaseline BP during a 13-month period. The treatment cohorts were consolidated into 4 therapeutic categories (OM, LOS, VAL, and IRB), and HCTZ was treated as a concomitant diuretic just like other diuretics that started during the baseline period. These consolidations were justified by the results of the preliminary analyses, which found that addition of HCTZ provides purely additive improvements in BP with no interactions noted with ARBs.

There were 3 multivariate regression models analyzed in this study: (1) analysis of covariance (ANCOVA) using the overall postbaseline SBP as the dependent variable, (2) ANCOVA using the overall postbaseline DBP as the dependent variable, and (3) logistic regression for JNC 7 goal attainment (yes/no).

The covariates considered to be in all of the above regressions were as follows:

- ARB cohort (LOS, VAL, IRB, or OM), combining ARB and ARB+HCTZ at index date
- Concomitant medication use: number of non-ARB antihypertensive classes used at baseline (ie, 0 ARB monotherapy; 1, 2, or 3 or more classes)
- Year of index date (2005 or later vs before 2005)
- Starting daily dose (high vs low: high doses were: 100 mg for LOS, 160 mg or 320 mg for VAL, 300 mg for IRB, and 40 mg for OM. Any lower doses were grouped as low)
- Baseline SBP (<140 mm Hg, 140–159 mm Hg [stage I], or ≥160 mm Hg [stage II])
- Baseline DBP (<90 mm Hg, 90–99 [stage I] mm Hg, or ≥100 mm Hg [stage II])
- Age (≤40 year, 41 to 65 years, and >65 years)
- Sex (male/female)
- Race (black, white, or missing/other)
- BMI (<25, 25 to <30 [overweight], ≥30 [obese], or missing)
- 6 yes/no-type covariates indicating whether the patient was diagnosed or treated with (1) ischemic heart disease, (2) heart failure, (3) cerebral vascular disease, (4) diabetes, (5) nephritis, or (6) CKD during the 13 months before the index date.

Baseline SBP was not used as a covariate for regression II and baseline DBP was not used for regression I. The same covariates were included for each of the subpopulation analyses except when a covariate had only one value for that subpopulation analysis, thus BMI would not be a covariate in the overweight or obese subpopulations.

All statistical analyses were completed using SAS software, version 9.2 (SAS Institute Inc, Cary, NC). For ANCOVA, the SAS GLM procedure was used, and the covariates for the final model were selected manually through backward elimination using P=.05. For logistic regression, the SAS LOGISTIC procedure was used, and the covariates for the final model were automatically selected using the stepwise process using SAS default entry and stay criteria (P=.05 for both). The ANCOVA used all eligible patients. The logistic regression for goal attainment excluded all patients who were already at the JNC 7 goal at baseline.

Treatment comparisons of BP reductions and goal attainment rates were performed for the following subgroups: African Americans, patients with diabetes, overweight patients, and obese patients.

RESULTS

Based on the patient selection criteria shown in Table I, a total of 73,012 hypertensive patients met the study inclusion criteria. The study sample characteristics are displayed in Table II and Table III. Diabetes was present in 28% of the population overall and CKD in <2%. The majority of the patients in each cohort were aged between 41 and 65 years and about 40% of the patients were older than 65 years. Use of concomitant antihypertensive drugs at baseline was widespread but was roughly similar across groups. Information on race was missing in about 60% of the patient charts; however, BMI information was available for all but 25% of the patients. The OM-treated patients had slightly higher average baseline BPs.

Preliminary Analyses

Figure 1 shows the BP changes from baseline during the 13-month follow-up period by treatment cohort using the quarterly mean changes. The OM cohort had consistently larger reductions in both SBP and

TABLE I. Final Study Population

Inclusion/Exclusion Criteria		Patient Count
EMR population		>11 million
Age 18 y and older		133,011
ARB or ARB+HCTZ combination		
Continuous activity (395 d prior and after date of earliest ARB prescription)		
February 1997 – November 2007		
Drop patients who had multiple different ARBs on same index day	−420	132,591
Drop patients who had no valid baseline BP reading (taken between day 30 and day 1 of index drug date) and no valid post-BP reading (day 6–395)	−14,002	118,589
Drop patients who had valid post-BP reading but no valid baseline BP reading	−21,970	96,619
Drop patients who had valid baseline BP reading but no valid post-BP reading	−3719	92,900
Drop patients whose baseline BP was <130/80 mm Hg	−15,475	77,425
Drop patients with non-study ARBs	−4,413	73,012

Abbreviations: ARB, angiotensin receptor blocker; BP, blood pressure; EMR, electronic medical record; HCTZ, hydrochlorothiazide.

DBP than all other ARB cohorts, and, similarly, the OM+HCTZ cohort also had consistently larger reductions in both SBP and DBP than all other ARB+HCTZ cohorts. Two further observations can be made from Figure 1:

- The difference between OM and other ARBs are about the same throughout all 5 quarterly time segments; therefore, it is reasonable to use the overall postbaseline BP, which is the average of the 5 quarterly averages, to study the treatment differences between OM and other ARBs.
- The differences between OM and other ARBs are similar whether HCTZ was added or not. Adding HCTZ increased the BP reduction by almost the same amount for each ARB; therefore, it is reasonable to combine the ARB group with the corresponding ARB+HCTZ group and treat HCTZ as an incremental effect in multivariate regressions.

Multivariate Analyses: Overall BP Changes From Baseline

The first few rows of Table IV show the treatment comparison results for the overall SBP and DBP changes from baseline for the consolidated ARB groups (ARB and ARB+concomitant antihypertensive medications such as HCTZ combined). All ARBs led to sustained reductions in BP during the 13-month follow-up, but there were significant differences in the magnitude of BP reduction. The raw mean SBP/DBP reductions with LOS, VAL, IRB, and OM were 9.3/4.9 mm Hg, 10.4/5.6 mm Hg, 10.1/5.3 mm Hg, and 12.4/6.8 mm Hg for all patients in the cohorts, and 10.2/5.8 mm Hg, 11.6/6.7 mm Hg, 11.2/6.0 mm Hg, and 14.3/8.3 mm Hg for the ARB monotherapy patients, respectively. Adjusting for all covariates, the reductions with OM were 1.88/0.86 mm Hg, 1.21/0.52 mm Hg, and 0.89/0.51 mm Hg more than for LOS, VAL, and IRB, for all patients, respectively (all P values $<.0001$).

Multivariate Analyses: JNC 7 BP Attainment Goal Rates

The last column of the first few rows of Table IV shows the raw JNC 7 goal attainment rates for each of the ARB groups overall. The number of patients used was slightly fewer than those used in BP change analyses because patients who were already at goal at baseline were excluded. The raw percentage of OM-treated patients who reached goal was between 4.6% and 9% higher than that of the other ARBs. Figure 2 (the 3 overall rows) show the treatment comparison results after adjusting for all the baseline covariates. The adjusted odds ratios (ORs) indicate that patients in the LOS, VAL, and IRB groups were 24%, 14%, and 9%, less likely to reach JNC 7 goal, respectively, than patients receiving OM. The 95% confidence intervals indicate that these advantages are all statistically significant at the .05 level.

Comparisons by Additional Classes of Antihypertensive Therapy

As noted in Table III, a large percentage of patients in each ARB-treated group also had additional classes of antihypertensive medications used concomitantly. Table IV and Figure 2 show the treatment comparisons by concomitant medication use. We analyzed subgroups with true ARB monotherapy (no additional antihypertensive use), 1 additional class of antihypertensive medications, 2 additional classes, or $\geq$3 additional classes of antihypertensives. With true ARB monotherapy, OM-treated patients showed the largest BP reduction and more of them attained JNC 7 goal than those in the other monotherapy ARB groups. During 13 months, on average, the adjusted differences in SBP/DBP for OM monotherpy was 2.43/1.16 mm Hg, 2.18/0.93 mm Hg, and 1.44/0.91 mm Hg compared with LOS, VAL, and IRB, respectively (all P values $<.0001$). With the addition of other antihypertensive agents, differences in SBP and DBP reductions between the ARB treatment groups do narrow; however, they remain significant for subgroups with 1 or 2 classes of concomitant antihypertensive medications. With the presence of $\geq$3 classes of concomitant antihypertensives, significant differences in SBP reductions persisted between OM and LOS and between OM and VAL but not between OM and IRB, and there were virtually no differences in DBP reduction among the ARBs.

TABLE II. Baseline Patient Characteristics

	Losartan (n=19,959), No. (%)	Valsartan (n=30,281), No. (%)	Irbesartan (n=9253), No. (%)	Olmesartan (n=13,519), No. (%)	Total (N=73,012), No. (%)
ARB as single agent	14,668 (20.09)	16,282 (22.30)	6754 (9.25)	9332 (12.78)	47,036 (64.42)
ARB+HCTZ	5291 (7.25)	13,999 (19.17)	2499 (3.42)	4187 (5.73)	25,976 (35.58)
Demographics					
Age, y					
18–40	1273 (6.38)	2309 (7.63)	651 (7.04)	1276 (9.44)	5509 (7.55)
41–65	10,181 (51.01)	15,486 (51.14)	4704 (50.84)	7366 (54.49)	37,737 (51.69)
>65	8505 (42.61)	12,486 (41.23)	3898 (42.13)	4877 (36.08)	29,766 (40.77)
Sex (male)	7775 (38.95)	11,836 (39.09)	3823 (41.32)	5610 (41.50)	29,044 (39.78)
Ethnicity					
White	6440 (32.27)	10,067 (33.25)	3137 (33.90)	4522 (33.45)	24,166 (33.10)
African American	1421 (7.12)	1958 (6.47)	452 (4.88)	7285 (5.39)	4559 (6.24)
Other/missing	12,098 (60.61)	18,256 (60.29)	5664 (61.21)	8269 (61.17)	50,418 (60.66)
BMI					
BMI 1 (<18.5, underweight)	67 (0.34)	104 (0.34)	23 (0.25)	48 (0.36)	242 (0.33)
BMI 2 (18.5–24.9, normal)	2136 (10.70)	3292 (10.87)	955 (10.32)	1483 (10.97)	7866 (10.77)
BMI 3 (25–29.9, overweight)	4434 (22.22)	7169 (23.67)	2155 (23.29)	3294 (24.37)	17,052 (23.36)
BMI 4 (≥30, obese)	7776 (38.96)	12,112 (40.00)	3585 (38.74)	5643 (41.74)	29,116 (39.88)
BMI missing	5546 (27.79)	7604 (25.11)	2535 (27.40)	3051 (22.57)	18,736 (25.66)
Comorbidities					
Ischemic heart disease	1151 (5.77)	1596 (5.27)	488 (5.27)	489 (3.62)	3724 (5.10)
Nephritis	614 (3.08)	831 (2.74)	300 (3.24)	355 (2.63)	2100 (2.88)
Cerebrovascular disease	633 (3.17)	851 (2.81)	297 (3.21)	359 (2.66)	2140 (2.93)
Diabetes	6273 (31.43)	8134 (26.86)	2930 (31.67)	3441 (25.45)	20,778 (28.46)
Chronic kidney disease	359 (1.80)	486 (1.60)	155 (1.68)	196 (1.45)	1196 (1.64)
Chronic heart failure	435 (2.18)	549 (1.81)	166 (1.79)	145 (1.07)	1295 (1.77)
Diabetes and chronic kidney disease	153 (0.77)	236 (0.78)	72 (0.78)	78 (0.58)	539 (0.74)
Baseline BP					
SBP, mean (SD)	147.5 (18.0)	148.3 (17.9)	146.9 (17.7))	148.7 (18.2)	148.0 (18.0)
DBP, mean (SD)	84.4 (11.6)	85.3 (11.7)	84.5 (11.5)	86.5 (11.9)	85.2 (11.7)

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; SBP, systolic blood pressure; SD, standard deviation.

The last column of Table IV shows the raw JNC 7 goal attainment rates by the number of classes of additional antihypertensives for each ARB. As the number of classes increases, both the raw goal attainment rates and the difference between OM and other ARBs decrease. The adjusted ORs of goal attainment for each of the ARBs vs OM are plotted in Figure 2. For ARB monotherapy, the ORs for LOS, VAL, and IRB compared with OM are 0.70, 0.74, and 0.83, respectively. These ORs increase in general as the number of classes of additional antihypertensives increases, meaning that the advantage of OM vs other ARBs are diluted as more medications, especially ≥3 classes, are added. However, for patients treated with losartan, the ORs always remain significantly lower than for OM, while for patients treated with VAL, no significant differences in OR remain after ≥3 classes of concomitant hypertension medications are present, and for IRB-treated patients, ORs were similar to OM once 2 classes of additional hypertensive medications were added to each group (Figure 2).

Multivariate Analyses: Subpopulations of Interest

Table IV and Figure 2 also show the treatment comparison results for BP reduction and JNC 7 goal attainment for some important subgroups of interest.

Overweight and Obese Patients. The results show that obese patients in each of the drug groups had less raw mean reduction in SBP and DBP than the overall population. While the mean differences of BP changes (and the magnitude of BP changes within each ARB treatment group) seem to be slightly less for obese patients than for overweight patients, patients taking OM showed significantly greater SBP/DBP reductions, eg, ranging from 2.49/1.28 to 1.77/0.86 vs LOS for overweight and obese patients, respectively. ORs of goal attainment for overweight patients in the LOS, VAL, and IRB groups were 0.75, 0.84, and 0.87, respectively, compared with those receiving OM, and in obese patients the ORs were 0.76, 0.89, and 0.91; however, the difference between OM and IRB was nonsignificant in obese patients.

TABLE III. Additional Baseline Characteristics

	Losartan (n=19,959)		Valsartan (n=30,281)		Irbesartan (n=9253)		Olmesartan (n=13,519)		Total (N=73,012)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Index year										
2005 or later	9028	45.2	14,995	49.5	4296	46.4	8552	63.3	36,871	50.5
Before 2005	10,931	54.8	15,286	50.5	4957	53.6	4967	36.7	36,141	49.5
Initial ARB dose										
High	4658	23.3	11,630	38.4	2637	28.5	4255	31.5	23,180	31.7
Low	14,672	73.5	16,422	54.2	6391	69.1	8870	65.6	46,355	63.5
Not available	629	3.2	2229	7.4	225	2.4	394	2.9	3477	4.8
Classes of non-ARB antihypertensives, No.										
0 (true ARB monotherapy)	4626	23.2	5841	19.3	2314	25.0	3332	24.6	16,113	22.1
1	6976	35.0	10,620	35.1	3155	34.1	4377	32.4	25,128	34.4
2	5127	25.7	8248	27.2	2274	24.6	3475	25.7	19,124	26.2
3 or more	3230	16.2	5572	18.4	1510	16.3	2335	17.3	12,647	17.3
Class of non-ARB antihypertensives										
Diuretics	8430	42.2	17,160	56.7	3824	41.3	6270	46.4	35,684	48.9
ACE inhibitors	6991	35.0	10,381	34.3	3250	35.1	4960	36.7	25,582	35.0
β-Blockers	5619	28.2	7913	26.1	2394	25.9	3620	26.8	19,546	26.8
Calcium channel blockers	4820	24.1	7407	24.5	2315	25.0	3167	23.4	17,709	24.3
Antiadrenergics, central	703	3.5	1005	3.3	324	3.5	470	3.5	2502	3.4
Antiadrenergics, peripheral	604	3.0	803	2.7	254	2.7	295	2.2	1956	2.7
α/β-Blockers	555	2.8	715	2.4	248	2.7	246	1.8	1764	2.4
Vasodilators	118	0.6	151	0.5	55	0.6	60	0.4	384	0.5
Reserpine	12	0.1	19	0.1	3	0.0	10	0.1	44	0.1
Selective aldosterone receptor antagonists	8	0.0	6	0.0	4	0.0	6	0.0	24	0.0
Direct renin inhibitors	0	0	4	0.0	4	0.0	2	0.0	0	0
Agents for pheochromocytoma	3	0.0	0	0	1	0.0	1	0.0	0	0

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

African American Patients. Mean SBP reductions were about 2 mm Hg less and goal attainment rates were more than 10% lower (in absolute value) for all treatment groups in the African American subpopulation than in the overall population for all the ARBs. But all point estimates of treatment comparisons vs OM, in both BP reduction and goal attainment, were similar to the overall population comparisons. Statistical significance for the ORs was achieved only in the comparison of OM with LOS, but not in the comparisons with VAL and IRB (except for SBP with VAL), perhaps due to smaller sample sizes for these subgroups.

Patients with Diabetes. As shown in Table IV, SBP and DBP reductions in patients with diabetes were about 1 mm Hg less than in the overall population. The JNC 7 goal attainment rates were much lower (about 15% to 20% lower in absolute value and close to 50% lower in relative value) than in the overall population due to the stricter requirement (<130/80 mm Hg, not <140/90 mm Hg) for this subgroup. While OM-treated patients had raw mean reductions of 11.1/5.4 during the 13-month follow-up, the LOS-treated patients had raw mean reductions of 8.4/4.2 mm Hg. Adjusted mean SBP/DBP differences between OM and LOS, VAL, and IRB were 1.70/0.65 mm Hg, 1.37/0.54 mm Hg, 0.88/0.40 mm Hg, respectively, (all were statistically significant). The ORs for goal attainment indicate that diabetic patients treated with LOS or VAL were less likely to get to goal (OR=0.78 and 0.84, respectively) compared with those treated with OM. However, the OR of goal attainment on IRB was not statistically significant (Figure 2).

DISCUSSION

In this study, BP reduction and JNC 7 goal attainment were assessed using chart data from clinical practice in ambulatory care. To our knowledge, this is the first large observational study evaluating comparative effectiveness of treatment modalities in hypertension using EMRs in community clinical practice.

Comparative Effectiveness

All the ARBs were effective in lowering BP and these reductions were sustained throughout the 13-month period of examination. Raw goal attainment rates ranged from 37.5% for the LOS cohort to 46.5% for OM.

The study findings reveal interesting similarities to results obtained in the clinical trial studies conducted

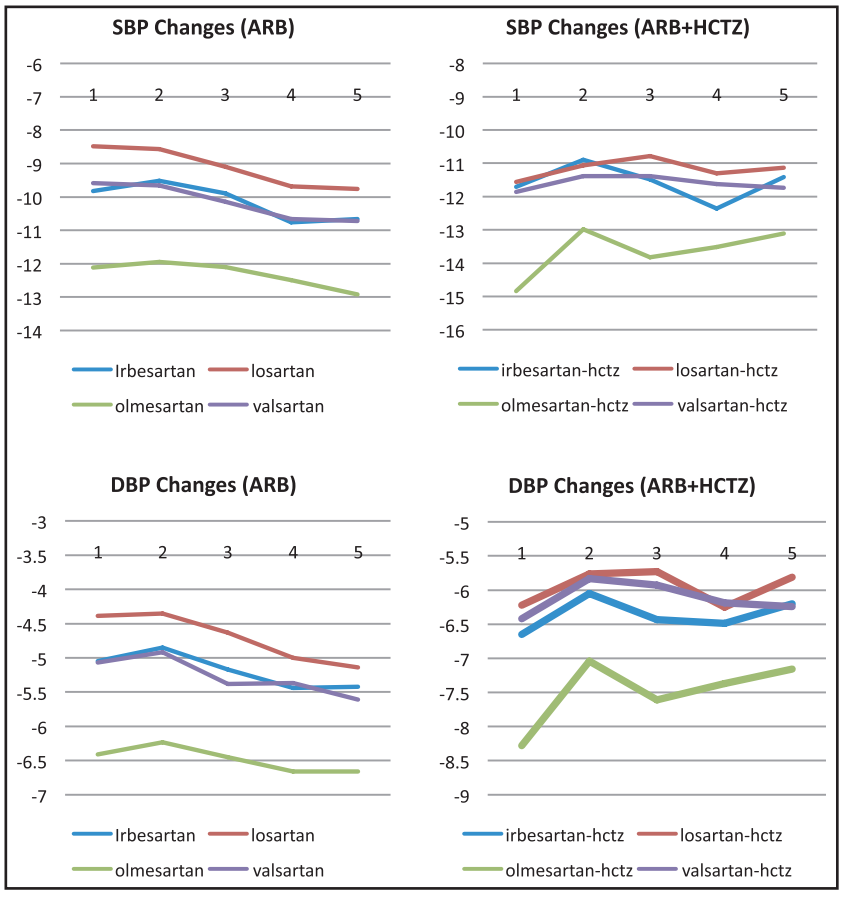

FIGURE 1. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) changes during 5 quarterly segments after initiating an angiotensin receptor blocker (ARB) or ARB+hydrochlorothiazide (HCTZ) therapy.

using the same treatment modalities. Results from randomized clinical trials that directly compared these therapies suggest that OM and IRB offer the greatest reduction in BP, followed by VAL and LOS.[21–25] The results of this study comparing the real-world effectiveness of ARBs in lowering DBP and SBP are consistent with those found in placebo-controlled head-to-head clinical trials comparing various ARBs.[24,25] In these clinical studies, however, not all doses of the drugs were studied and the follow-up period was often limited. The current study extends these clinical trial findings and the analyses conducted extend our understanding of the comparative effectiveness of the targeted agents through deeper evaluation of specific subgroups of interest: African Americans, patients with diabetes, and those who are overweight or obese. In these subpopulations, greater rates of goal attainment with OM were seen, in a pattern that is consistent with the overall population studied (Figure 2). In addition, a recent cost-effectiveness study based on actual patient charts associated with a large national claims database also found greater goal attainment rates for OM, followed by IRB, VAL, and LOS. In that study, however, only about 1200 charts were examined, compared with the 73,000 charts in this study.[19] Comparative effectiveness research as done in this study represents a practical and cost-effective way to complement randomized clinical therapeutic trials, extending the observational period as well as the types of patients studied.

Impact of Concomitant Medication Use

In the overall population, the combined analysis suggests that patients treated with OM have statistically significantly greater reductions in SBP and DBP and higher rates of JNC 7 goal attainment compared with patients taking LOS, VAL, or IRB. A very large proportion of patients treated with ARBs also have other concomitant medications on board, ranging from one additional class of antihypertensive agent to >5. We investigated the impact of these concomitant therapies on patient BP outcomes. The use of concomitant antihypertensive therapies is associated with progressively smaller treatment effects in both BP reduction and JNC 7 goal attainment in this study. This is perhaps a result of different patient populations, as more

TABLE IV. Mean BP Change and JNC 7 Goal Attainment Rates

		Mean BP Change From Baseline							JNC 7 Goal Attainment	
			SBP			DBP				
				Adjusted Difference vs OM			Adjusted Difference vs OM			
Population	Index ARB	No.	Raw Mean Change	Mean	*P* Value	Raw Mean Change	Mean	*P* Value	No.	Raw Rate, %
Overall (all patients)	LOS	19,959	−9.3	1.88	<.0001	−4.9	0.86	<.0001	16,522	37.5
	VAL	30,281	−10.4	1.21	<.0001	−5.6	0.52	<.0001	25,116	41.3
	IRB	9253	−10.1	0.89	<.0001	−5.3	0.51	<.0001	7657	41.9
	OM	13,519	−12.4			−6.8			11,268	46.5
Classes of additional antihypertensives, No.										
0 (ARB monotherapy)	LOS	4626	−10.2	2.43	<.0001	−5.8	1.16	<.0001	3812	42.7
	VAL	5841	−11.6	2.18	<.0001	−6.7	0.93	<.0001	4937	45.2
	IRB	2314	−11.2	1.44	<.0001	−6.0	0.91	<.0001	1972	47.1
	OM	3332	−14.3			−8.3			2860	54.1
1	LOS	6976	−9.3	2.79	<.0001	−5.0	1.34	<.0001	5643	39.3
	VAL	10,620	−11.0	1.93	<.0001	−6.2	0.81	<.0001	8680	46.3
	IRB	3155	−10.1	1.64	<.0001	−5.5	0.86	<.0001	2517	44.6
	OM	4377	−13.3			−7.5			3591	50.8
2	LOS	5127	−8.7	1.67	<.0001	−4.6	0.74	<.0001	4247	37.2
	VAL	8248	−9.6	1.09	<.0001	−4.8	0.68	<.0001	6715	39.2
	IRB	2274	−9.1	0.99	.0067	−4.9	0.50	.0213	1868	39.3
	OM	3475	−10.8			−5.8			2830	43.1
≥3	LOS	3230	−8.8	1.30	.0004	−4.0	0.32	.1366	2820	27.4
	VAL	5572	−9.3	1.01	.0025	−4.4	0.07	.7348	4784	31.0
	IRB	1510	−9.7	0.03	.9537	−4.5	−0.16	.5513	1300	32.9
	OM	2335	−10.4			−4.7			1987	32.9
Overweight (BMI 25–<30 kg/m^2)	LOS	4434	−9.5	2.49	<.0001	−4.7	1.28	<.0001	3545	42.2
	VAL	7169	−11.0	1.49	<.0001	−5.8	0.67	<.0001	5813	46.0
	IRB	2155	−10.2	1.16	.0019	−5.2	0.83	.0002	1737	46.5
	OM	3294	−13.0			−7.2			2685	51.6
Obese (BMI ≥30 kg/m^2)	LOS	7776	−8.4	1.77	<.0001	−4.8	0.86	<.0001	6616	34.8
	VAL	12,112	−9.7	1.20	<.0001	−5.6	0.54	<.0001	10,225	39.2
	IRB	3585	−9.3	0.95	.001	−5.3	0.57	.0009	3046	38.7
	OM	5643	−11.2			−6.5			4761	43.8
African Americans	LOS	1421	−7.6	1.89	.0021	−4.6	0.74	.0417	1271	25.7
	VAL	1958	−8.7	1.19	.0411	−4.9	0.37	.2896	1731	29.6
	IRB	452	−8.3	0.89	.2677	−4.5	0.74	.1219	400	27.3
	OM	728	−10.9			−6.3			654	35.2
Patients with diabetes	LOS	6273	−8.4	1.70	<.0001	−4.2	0.65	.0001	6273	21.7
	VAL	8134	−9.3	1.37	<.0001	−4.5	0.54	.0009	8134	21.8
	IRB	2930	−8.9	0.88	.0094	−4.4	0.40	.0474	2930	25.3
	OM	3441	−11.1			−5.4			3441	25.2

Abbreviations: ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; IRB, irbesartan; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; LOS, losartan; OM, olmesartan medoxamil; SBP, systolic blood pressure; VAL, valsartan.

concomitant antihypertensive medications may indicate harder-to-treat patients. The advantage of OM is also diluted as more, especially ≥3, additional antihypertensives are present.

Clinical Significance

The findings of this study provide an opportunity for evaluating the clinical significance and relevance of such research. While statistical significance is reported, it is critical to place these results within the framework of a meaningful clinical difference for patients. Staessen and colleagues[26] reported that differences in SBP reductions ranging from 2.0 mm Hg up to 15 mm Hg can produce meaningful and significant reductions in cardiovascular outcomes including cardiovascular mortality, stroke, and myocardial infarction. Their meta-analysis revealed that between-group SBP differences of 2.0 mm Hg, 2.2 mm Hg, and 2.3 mm Hg may

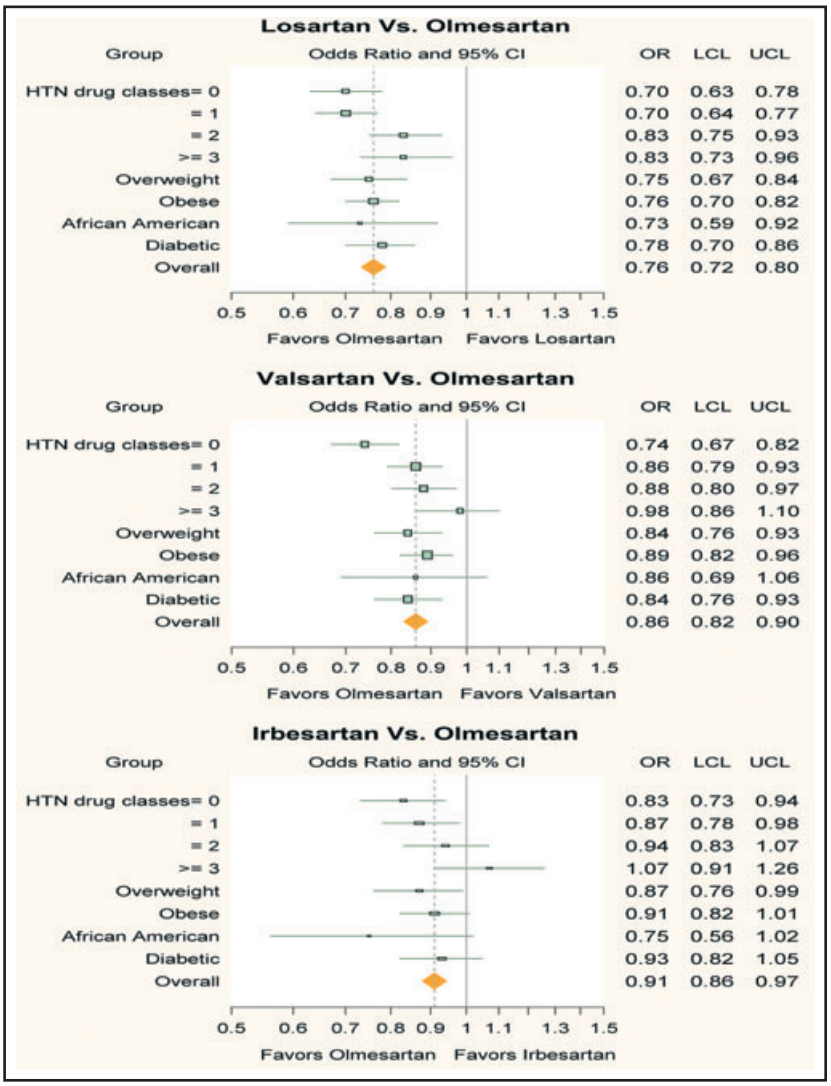

FIGURE 2. Adjusted odds ratio (OR) comparisons for blood pressure goal attainment rates. HTN drug classes indicates additional classes of antihypertensive medications taken concomitantly; CI, confidence interval; LCL, lower control limit; UCL, upper control limit.

lower the odds of observed cardiovascular events by between 2% and 30%.[26] In the present analysis, OM monotherapy patients had an adjusted mean difference in SBP of 2.43 mm Hg and 2.18 mm Hg compared with LOS and VAL monotherapy patients, sustained during the 13-month follow-up. In other subgroups, such as patients with 1 class of concomitant antihypertensive therapy and overweight patients, OM-treated patients had an adjusted mean SBP reduction that was 2.79 mm Hg and 2.49 mm Hg greater than for similar LOS-treated patients during 13 months. Whether these sustained population-wide differences in SBP in the OM-treated groups will lead to improvements in cardiovascular outcomes was not studied, but should be considered in clinical decision-making.

The risk of incident atrial fibrillation also increases with increasing SBP, and patients with SBP >140 mm Hg account for more than 82% of the increase in incident atrial fibrillation. The significant differences in goal attainment observed in this study, ie, SBP reductions <140 mm Hg, should be considered in treatment choice as well. Goal attainment was observed during a 13-month period, and results indicate that OM exhibited a consistent advantage on the rate of goal attainment for patients. Goal attainment ORs in the 3 ARB monotherapy cohorts were approximately 30% to 17% lower than the OM monotherapy cohort, and similar trends, of lesser magnitude, were observed with the presence of concomitant antihypertension drugs. In a 12-year observational study of 940 hypertensive patients, sustained BP control (BP 140/90 mm Hg) resulted in significantly fewer cardiovascular events for both men and women. When BP was controlled, the incidence of coronary and cerebrovascular events was 15% in men and 9% in women, vs 36% in men and 12% in women with uncontrolled hypertension.[27]

The results in the current study, while covering a modest 13-month duration, suggest that at comparable doses and baseline BP levels, OM has the greatest likelihood to get patients to goal, and this result is consistent across all subpopulations studied. Thus, several of the statistically significant differences noted in this study do seem to have clinical significance as well.

Results in Subpopulations Studied

With the exception of LOS monotherapy, treatment with all other ARBs exceeded (OM) or approached (VAL, IRB) a 10-mm Hg reduction in mean SBP during the 13 months of this study. Patients treated with OM consistently achieved at least a mean 10-mm Hg SBP reduction in all subgroups and at least a mean 5-mm Hg DBP reduction in all but one subgroup. In the obese, African American, and diabetic subgroups, only OM was associated with a reduction of this magnitude. Data from a meta-analysis of 147 randomized trials containing a total of 464,000 patients showed a 24% decrease in fatal and nonfatal coronary heart disease events, and a 33% decrease in the incidence of stroke was accomplished by lowering SBP 10 mm Hg. Furthermore, in 71 BP difference trials, a reduction in 10 mm Hg systolic and 5 mm Hg diastolic were associated with a 22% reduction in coronary heart disease events and a 41% reduction in stroke events.[27]

While DBP reductions of about 5 mm Hg are achieved by all the ARBs, subgroups of patients on monotherapy with OM reduced DBP by about 8.3 mm Hg, and patients combining OM with 1 other concomitant antihypertensive medication also showed a reduction of 7.5 mm Hg. However, for the overall population studied, none of the other ARB treatment groups showed greater than a 6.7 mm Hg reduction in DBP during 13 months. It has been reported that a 7.5-mm Hg reduction in DBP is associated with a risk reduction of 21% in coronary heart disease and 46% in stroke.[28] The French League Against Hypertension[26] also reported that a 5 mm Hg to 6 mm Hg reduction in DBP is linked to 38% fewer cerebral vascular accidents, as well as 16% fewer cardiovascular-related complications, including death.

This study also confirms that goal attainment for African Americans and for patients with diabetes is more difficult than for the overall population. Obese and overweight patients, by contrast, showed BP reductions and goal attainment rates more in keeping with the overall population. An important finding of this study was the consistency with which OM-treated patients showed both greater BP reductions and goal attainment rates after adjusting for baseline differences. In other words, the results in the subpopulations follow the differences seen in the overall population. However, statistical significance was not achieved in African American and diabetic subgroups particularly against IRB. Some of this may be due to smaller sample sizes (such as for the African Americans), but may also indicate that these drugs have similar effectiveness.

The importance of confirming clinical trial results in the larger population of patients receiving usual care is that this real-world information can provide clinicians with decision support relevant to their office practice with patients. Clinical trials generally enroll healthier, younger, compliant patients and the results may not be reflected in clinical practice where older, sicker, noncompliant patients with multiple medical conditions are seen. The present results provide some confidence that significant control of BP seen in the controlled-environment short- and long-term clinical trials with these agents also play out in practice during a 13-month follow-up in a very diverse population as encountered in clinical practice. These particular findings also offer the opportunity to evaluate the comparative effectiveness of treatment modalities across time and to assess the persistence of treatment effect for all patients and particularly for those with specific risk factors and concomitant comorbidities known to lead to cardiovascular sequalae. Finally the differences in magnitude of the BP goal attainment and ORs observed here points to the treatment options that can offer patients the opportunity to achieve their BP attainment goal.

LIMITATIONS

There are several limitations to the current study. This was a retrospective observational study and, as such, assignment to treatment group was a function of clinical assessment by the individual's physician and not a randomized requirement of the study protocol. Since there are important differences in the indications for ARBs, this is an important limitation. Although continuous activity was monitored for at least 13 months before and after the index event of the first ARB, it was impossible to determine whether a patient received an antihypertensive prescription from another physician (which was not recorded in the EMR database).

Numerous covariates were accounted for in the ANCOVA and logistic regression analyses, ranging from starting dose of ARB and specific comorbidities to number of concomitant medications, baseline SBP, DBP, and patient characteristics such as BMI, race, and age. Nevertheless, certain comorbidities such as CKD or diabetes may be underdiagnosed and underreported in the database. Moreover, information on race was missing from approximately 60% of the records, so it is unclear whether race was adequately controlled for in this study. However, "race" was missing at roughly the same rate in all the treatment cohorts, so it is unlikely that it systematically biased the findings. It is possible that there were other differences between the cohorts that were not observable in the database. Compliance and persistence are important information and these were not available in the database—pharmacy dispensing and refilling, commonly available in a

claims database, are not available in a primary care clinical record. However, there appears to be no reason to assume systematic differences in compliance or persistence between the ARBs, given their similar tolerance profile. We also accounted for a historic or time effect in this study by adjusting for year of index date (prior to 2005 or 2005 or after), since it was believed that a greater emphasis by physicians on the goals of 140/90 mm Hg likely occurred after JNC 7 was issued in 2003. The 2005 time-point roughly divided our population into two equal halves. The logistic regression confirmed that the effectiveness differences seen in the ARB treatment groups were not simply a byproduct of this historically later emphasis on goals.

Collection of information on the side effects of medications and other specific health issues or sequalae that may result from uncontrolled hypertension were not consistently available in the chart data, as the EMR is a record of the outpatient encounter in the physician office and side effects may not be recorded consistently. Further, occurrence of acute health care service events, such as emergency department visits or hospitalizations, were not available in the primary care data source. Even in light of these limitations, the benefits of this study should be placed within the context of the real-world data source from which the analyses were derived.

CONCLUSIONS

Observational studies such as ours, mining a large EMR database, may have important therapeutic implications in the practice of medicine. It should be recalled that in the pre-EMR era, observational studies yielded public health information on information such as tobacco consumption and hormone replacement therapy. The EMR-derived data applying comparative effectiveness research, as performed in this study, might yield similar useful information with implications for the optimal treatment of hypertension. In the clinical treatment context, with only about one half of patients treated reaching BP reduction goal[19] consistent with JNC 7 goal attainment guidance,[17] the need to inform practitioners and payers of the comparative effectiveness of current treatment modalities is brought into clear focus. Based on these current findings from ambulatory care settings across the United States, wider application of treatment modalities such as OM may yield consistently improved BP outcomes for patients with hypertension, with or without concomitant medications. Assuring equal access to a broad range of ARB therapies or providing preferred status to more effective therapies are both options that should be considered by health plans in light of these findings.

Utilizing available therapies for hypertension, we should continue the global efforts to achieve recommended goal BP targets in patients with hypertension. Even a modest downward shift in the attained BP levels, sustained over time, offers enormous health benefits and protection against cardiovascular disease, CKD, and stroke in patients with hypertension.

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