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Original article

Chart review of patients on valsartan-based single-pill combinations vs. ARB-based free combinations for BP goal achievement

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Abstract

Objective:
To compare blood pressure (BP) goal achievement associated with the use of valsartan-based single pill combinations (SPCs) vs. angiotensin II receptor blocker (ARB)-based free combinations (FCs) among adult hypertension patients.

Research design and methods:
Data were collected from physician-administered chart review of adult hypertension patients in the South Central region. All patients had uncontrolled BP before initiating one of the index therapies (SPCs: valsartan/amlodipine or valsartan/hydrochlorothiazide [HCTZ], FCs: ARB + calcium channel blocker [CCB] or ARB + HCTZ) between 07/2008 and 06/2009. Up to three BP measures were collected starting from 45 days after the therapy initiation. BP goal was <130/80 mmHg for patients with diabetes, chronic renal disease or coronary heart disease; or <140/90 mmHg for patients without these comorbidities. The Kaplan–Meier method with log-rank test was used to compare rates of BP goal achievement associated with valsartan-based SPCs vs. ARB-based FCs over time. Cox proportional hazard models were used to estimate the likelihood of BP goal achievement associated with SPCs vs. FCs, controlling for demographics, baseline BP, hypertension history, comorbidities, prior and concurrent use of anti-hypertensive medications, and physician specialty.

Results:
The study included 812 patients: 414 on valsartan-based SPCs (209 on valsartan/amlodipine and 205 on valsartan/HCTZ) and 398 on ARB-based FCs (200 on ARB + CCB and 198 on ARB + HCTZ). The ARBs in the FC group included valsartan, losartan, olmesartan, telmisartan, irbesartan and candesartan. In the ARB FC group, the most commonly used ARB and CCB were valsartan (29.1%) and amlodipine (81.5%), respectively. During the observation period (81 days for valsartan SPC patients and 90 days for ARB FC patients), 65.9% of valsartan SPC patients and 55.8% of the ARB FC patients achieved BP goal. Over time, the rates of BP goal achievement were consistently higher among valsartan SPC vs. ARB FC patients ($p = 0.01$): 31.1% vs. 28.9% and 69.1% vs. 59.2% at month 3 and 6 after therapy initiation, respectively. Cox regression confirmed that valsartan SPC patients were more likely to achieve BP goal (HR = 1.22; $p = 0.05$). A similar trend was observed in the subgroup analyses comparing SPC of valsartan/amlodipine vs. FCs of ARB + CCB and SPC of valsartan/HCTZ vs. FCs of ARB + HCTZ.

Limitations:
Non-randomization of treatments, limited generalizability, and no records of BP measures within 45 days.

Conclusions:
Patients using valsartan-based SPCs were significantly more likely to achieve BP goal than those treated with ARB-based FCs in the real-world clinical practice in the South Central region. The significance was achieved at two-sided $\alpha = 0.05$.

Introduction

Abundant clinical evidence has established the importance of controlling hypertension in order to prevent end organ damage and complications[1]. Clinical guidelines, including the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7), have established the goal for hypertension treatment: for most patients, blood pressure (BP) should be maintained at the systolic/diastolic pressure of <140/90 mmHg; for patients with diabetes, chronic kidney disease, or coronary heart disease, the goal of therapy is <130/80 mmHg[1–3]. Despite the guidelines, epidemiological studies have demonstrated that the majority of patients with hypertension do not achieve adequate systolic/diastolic blood pressure control[4–6].

Because of the complexity of BP physiology, disease progression and increasing lifespan, most hypertensive patients will require a combination of different classes of antihypertensive drugs either in single pill combination (SPC) or free combination (FC) to achieve the BP goal[1,7,8]. In the management of hypertension, patient compliance with treatment is essential for achieving optimal clinical outcomes and maintaining long-term therapeutic goals. SPC antihypertensive medications reduce the complexity of a treatment regimen and increase the convenience for patients, especially older patients for whom polypharmacy is common. SPC products have been shown to increase patient compliance and persistence[9–13] and reduce health care costs[8,11–17] compared with their corresponding free combinations (i.e., the same drug classes in separate pills) at national and state level. The differences in compliance and health care costs observed in the previous studies may be attributable to the different drug forms between SPCs vs. FCs. They may also result from different ingredients in SPCs vs. FCs. Although a previous study showed that higher compliance was associated with better blood pressure control in patients receiving monotherapies[18], whether the improved compliance associated with SPC use can actually lead to better BP control has not yet been examined.

The existing evidence on the effectiveness of SPCs vs. FCs appears to be limited to clinical trials. However, even in clinical trial setting, the evidence is limited because the majority of randomized clinical trials were conducted with free combinations rather than SPCs when the SPC formulations were still in the development. Among the existing trials comparing SPCs vs. FCs, the ones conducted earlier (mostly conducted around the 1980s) generally focused on beta-blockers and diuretics and showed no significant difference in BP control between SPC and FC therapies[19–23]. However, one recent clinical trial by Mancia and colleagues demonstrated significantly better efficacy associated with SPCs compared to FCs[24]. They found that a higher proportion of patients treated with SPC of candesartan cilexetil/HCTZ achieved blood pressure goal than patients who received FCs of HCTZ added to the previous monotherapy they had received. In addition, a separate clinical study showed that the SPC of valsartan 160 mg/HCTZ 25 mg significantly reduced diastolic blood pressure by 5.1 ± 7.9 mmHg and systolic blood pressure by 3.4 ± 13.0 mmHg in patients whose BP had been inadequately controlled by the previous treatment with FC of candesartan 32 mg and HCTZ 25 mg[25]. Because data from the clinical trials may not necessarily reflect the treatment effectiveness in clinical practice, research is needed to assess the BP goal achievement of SPC vs. FC antihypertensive regimens in real-world clinical care.

The objective of this observational study was to compare BP goal achievement in hypertensive patients who were initiated on or switched to valsartan-based SPCs versus ARB-based FCs of the same classes using an online chart review conducted by physicians in the South Central region in the United States.

The study was designed to compare the effect of the most commonly prescribed ARB-based SPCs versus ARB-based FCs of the same classes on BP goal achievement in the real world. Therefore, valsartan-based SPCs, including SPC of valsartan/amlodipine and valsartan/HCTZ, were selected into the ARB-based SPC group. In the ARB-based FC group, all ARB-based FCs of the same classes (i.e., ARB + CCB and ARB + HCTZ) were included. The study did not restrict the comparison group to valsartan-based FCs because in the real world, all free combinations of ARB + CCB and ARB + HCTZ are the FC alternatives to the valsartan-based SPCs.

The study focused on the South Central region because the prevalence rates of cardiovascular diseases and associated mortality, including the prevalence of hypertension and hypertension-related mortality, are higher in many southern states (e.g., Alabama, Arkansas, Louisiana, Mississippi, Tennessee and Texas) than in other states[26]. This study was expected to provide more real-world practice evidence to guide effective BP control in this region. Other regions with high prevalence of hypertension and cardiovascular diseases and similar demographic compositions as in the South Central region may also refer to the study findings. However, decision making should be based on the specific scenarios in individual regions, which may require separate analysis using region-specific data.

Patients and methods

Study sample

This study was based on a chart review of hypertensive patients who received valsartan-based SPC or FCs of ARB + calcium channel blocker (CCB) or

ARB + hydrochlorothiazide (HCTZ) (referred to as index therapy). Primary care physicians (PCPs), including internists, and cardiologists in the nine states of the South Central region (Texas, Alabama, Mississippi, Missouri, Louisiana, Kansas, Tennessee, Arkansas, Oklahoma) in an existing physician panel were recruited to participate in the study by a vendor specialized in online physician surveys (All Global Ltd, New York, NY). The existing panel of physicians was selected to be representative of the physicians in the U.S. in geographic locations, specialties, urban vs. rural setting, and hospital vs. office-based practice. A stratified random sampling approach was used to recruit physicians to the panel. Specifically, physicians listed in the directory of the American Medical Association were first stratified by geographic location, specialty, urbanicity and practice type. Within each stratum defined by the combination of the aforementioned characteristics, physicians were randomly selected and recruited by telephone calls to opt in the physician panel. In this study, PCPs and cardiologists in the existing South Central region panel were randomly selected and contacted by email to participate in this study. Therefore, assuming there were no systematic differences between PCPs and cardiologists who agreed to participate in this study vs. those who declined, the physicians in our study were representative of all PCPs and cardiologists in the South Central region in the US.

In the current study, each participating physician was asked to select five hypertensive patients who met the inclusion criteria and provide patient information using an online chart abstraction form. To maximize the randomness in patient selection, physicians were asked to choose each eligible patient whose last name began with a computer-generated random letter. If the physician did not have a patient whose last name began with the letter, a patient whose name started with the next closest letter in the alphabetical order was selected.

Patients were considered eligible for this study if they met the following inclusion criteria: (1) patients had to be at least 18 years or older when they were initiated on or switched to any of the four combination antihypertensive therapies (index therapy) between July 1, 2008 and June 30, 2009: SPC of valsartan/amlodipine, any FC of ARB + CCB, SPC of valsartan/HCTZ, and any FC of ARB + HCTZ; (2) patients must have had high BP (systolic BP $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg) within one month prior to the initiation of the index therapy; and (3) patients must have had at least one BP reading beyond 45 days after the initiation of the index therapy.

To ensure the balance of the sample size across the four index therapies, a stratified random sampling framework was used. The strata were defined by both index therapy and type of physicians (PCPs vs. cardiologists). Our goal was to recruit enough patients in each index therapy group so that the study was powered to identify a hazard ratio (HR) of 1.1 between each type of valsartan-based SPC vs. its corresponding ARB-based FC of the same classes using log-rank tests (i.e., comparison of SPC of valsartan/amlodipine vs. FC of ARB + CCB or comparison of SPC of valsartan/HCTZ vs. FC of ARB + HCTZ). We assumed that the BP goal achievement rate associated with valsartan-based SPCs was 65%, which was approximately 15% lower than the reported BP goal achievement rate for ARB-based SPC in the clinical trial[24]. With a two-tailed α level of 0.05 and β of 0.1, 173 patients would be required for each index therapy group to detect a significant difference of HR = 1.1 in log-rank tests. In this study, we collected information on approximately 200 patients in each index therapy group.

In the chart review, the participating physicians were required to provide treatment and BP data using a standardized chart abstraction form, which collected information on up to three consecutive BP readings after the 45th day since the initiation of the index therapy as well as the dates on which the BP readings were obtained. The 45 days after the index therapy initiation was chosen because based on JNC7 recommendation, most patients should return for follow-up and adjustment of medications at monthly intervals after treatment initiation[1]. The additional 15 days were added to allow for variations in follow-up monitoring in the real-world. In addition, BP measurements obtained from 45 days after treatment initiation onward were likely to reflect patients' stabilized BP level during follow-up care.

Information on patient's age, gender, race/ethnicity, history of hypertension, baseline BP before the initiation of the index therapy, comorbidities, and prior and current medications was also collected. The chart abstraction form did not include any information that can be linked to a patient's identity, such as name, date of birth, and social security number, and the database was HIPAA compliant.

Measures for BP goal achievement

The primary end point of this study was BP goal achievement, which was defined based on the guidelines from JNC7 and the American Heart Association/American College of Cardiology[1–2]:

(1) Adult hypertension patients with diabetes, chronic renal disease or coronary heart disease: systolic BP < 130 mmHg *and* diastolic BP < 80 mmHg
(2) Adult hypertension patients without the above comorbidities: systolic BP < 140 mmHg *and* diastolic BP < 90 mmHg

A patient was considered to achieve BP goal if at least one BP measure met the above criteria while the patient was on the index therapy. If a patient had more than one BP

reading after the 45th day that met the goal, the first date of achieving BP goal was considered the goal achievement date. Time from the 45th day since therapy initiation to BP goal achievement date was calculated. If patients did not achieve BP goal while on index therapy, they were censored at the earliest date of the following events: (1) discontinuation of the index therapy; (2) the last date when BP was recorded in the data; (3) loss to follow-up.

Statistical analysis

Patients' demographics, baseline characteristics, and physician's specialty were summarized and descriptively compared between patients who were started on the valsartan-based SPCs and patients who were started on the ARB-based FC regimens.

Crude rate of BP goal achievement was calculated for valsartan SPC vs. ARB FC-treated patients, respectively, during the observation period, defined as the time period from the 45th day after the index therapy initiation to the BP goal achievement date or a censoring event, whichever came first. In addition, Kaplan–Meier analysis was used to estimate the rates of BP goal achievement over time among patients who were initiated on valsartan SPCs and ARB FCs. Patients were censored at the earliest date of the following events: (1) discontinuation of the index therapy; (2) the last date when BP was recorded in the data; (3) loss to follow-up. Log-rank tests were used to compare the rates of BP goal achievement between patients on valsartan SPCs and those on ARB FCs.

Furthermore, multivariate regression analysis was applied in patients on valsartan SPC and on ARB FC regimens. Cox proportional hazard models were used to estimate the likelihood of achieving the BP goals among patients receiving valsartan SPCs vs. those receiving ARB FCs while controlling for patients' demographics, BP level above the normal standard at baseline, hypertension history, comorbidities, prior use of combination therapy, and concurrent use of any other antihypertensive medications. The same censoring point in the Kaplan–Meier analysis was applied in the Cox proportional hazard models as well. Because multiple patients were treated by the same physician, the models also accounted for physician clustering effect by adjusting for the covariance matrix.

The above analyses were repeated for subgroup comparing the SPC of valsartan/amlodipine vs. FCs of ARB + CCB as well as the SPC of valsartan/HCTZ vs. FCs of ARB + HCTZ.

All analyses were conducted using SAS Version 9.2. An a priori two-tailed α level of 0.05 was used for statistical inference.

Results

Patient baseline characteristics

A total of 163 primary care physicians and cardiologists participated in the study and provided chart review data. Each physician provided data on five patients. Two patients were excluded because they did not receive one of the four index therapies defined in this study. One patient was excluded because of missing date for BP measurement and drug discontinuation date. As a result, 812 patients were included in the analysis. Among these patients, 414 were started on the valsartan-based SPC antihypertensive drugs, including 209 on valsartan/amlodipine and 205 on valsartan/HCTZ. The other 398 patients were started on ARB-based FCs, including 200 patients receiving ARB + CCB and 198 receiving ARB + HCTZ (Table 1). Valsartan was the most commonly used ARB for ARB + CCB and ARB + HCTZ FC-treated patients (29.1%), followed by losartan (24.9%) and olmesartan (20.1%). The most commonly prescribed CCB in the FCs of ARB + CCB was amlodipine (81.5%).

Baseline demographics, history of hypertension, baseline BP, prior and concurrent antihypertensive treatments and type of physicians were similar between patients treated with the valsartan SPCs and those treated with ARB FC regimens. The mean age of the overall sample was approximately 55 years (Table 1). At baseline, the valsartan SPC- and ARB FC-treated patients were on average 23.9 and 24.5 mmHg above their systolic BP goal, respectively; and 9.1 and 9.4 mmHg above their diastolic BP goal, respectively. The proportion of patients with a history of hypertension for at least 10 years was 19.8% for patients on valsartan SPCs and 24.1% for patients on ARB FCs, which was not significantly different ($p = 0.14$). However, the subgroup of valsartan/amlodipine SPC-treated patients had a higher proportion of patients with hypertension for at least 10 years compared with ARB + CCB FC-treated patients (20.1% vs. 32.5%, $p < 0.01$). Overall, prior use of combination antihypertensive therapy was more common in the valsartan SPC-treated patients than in the ARB FC-treated patients (32.1% vs. 25.9%, $p = 0.05$). The proportion of patients under the care of cardiologists vs. primary care physicians did not differ significantly between valsartan SPC- and ARB FC-treated patients or between subgroups.

The prevalence of comorbidities was balanced between patients on valsartan-based SPCs and ARB-based FCs, with the exception of chronic renal disease, which was present in 5.1% of the valsartan SPC-treated patients and 11.3% of the ARB FC-treated patients ($p < 0.01$). Chronic renal disease was also more common among patients on the FCs of ARB + HCTZ than those on the SPC of valsartan/HCTZ (10.6% vs. 3.4%, $p < 0.01$).

Table 1. Baseline characteristics of patient sample.

Variable	Single Pill Combination (SPC)			Free Combination (FC)			*P* value		
	Valsartan/ amlodipine [A]	Valsartan/HCTZ [B]	All SPCs [A] + [B]	ARB + CCB [C]	ARB + HCTZ [D]	All FCs [C] + [D]	[A] vs. [C]	[B] vs. [D]	[A + B] vs.[C + D]
N	209	205	414	200	198	398			
Demographics									
Age (years), mean (SD)	54.9 (11.3)	54.9 (12.2)	54.9 (11.7)	55.7 (11.8)	54.4 (12.5)	55.1 (12.1)	0.47	0.88	0.68
Elderly (≥65 y) *n* (%)	39 (18.7%)	49 (23.9%)	88 (21.3%)	45 (22.5%)	40 (20.2%)	85 (21.4%)	0.34	0.37	0.97
Female, *n* (%)	74 (35.4%)	89 (43.4%)	163 (39.4%)	78 (39.0%)	81 (40.9%)	159 (39.9%)	0.45	0.61	0.87
African American, *n* (%)	52 (24.9%)	49 (23.9%)	101 (24.4%)	56 (28.0%)	50 (25.4%)	106 (26.7%)	0.47	0.73	0.45
History of hypertension									
≥10 years, *n* (%)	42 (20.1%)	40 (19.5%)	82 (19.8%)	65 (32.5%)	31 (15.7%)	96 (24.1%)	<0.01*	0.30	0.14
Unknown, *n* (%)	8 (3.8%)	12 (5.9%)	20 (4.8%)	11 (5.5%)	11 (5.6%)	22 (5.5%)	0.42	0.90	0.65
Baseline BP over goal (mm Hg)									
Systolic, mean (SD)	24.9 (12.9)	22.9 (15.1)	23.9 (14.1)	26.8 (15.0)	22.2 (13.9)	24.5 (14.6)	0.56	0.84	0.69
Diastolic, mean (SD)	10.0 (8.3)	8.1 (7.9)	9.1 (8.1)	10.5 (9.2)	8.2 (8.3)	9.4 (8.8)	0.72	0.88	0.85
Prior and concurrent medications									
Prior use of combination therapy, *n* (%)	88 (42.1%)	45 (22.0%)	133 (32.1%)	70 (35.0%)	33 (16.7%)	103 (25.9%)	0.14	0.18	0.05*
Concurrent use of other antihypertensives, *n* (%)	70 (33.5%)	48 (23.4%)	118 (28.5%)	64 (32.0%)	52 (26.3%)	116 (29.1%)	0.75	0.51	0.84
Comorbidities									
Diabetes, *n* (%)	64 (30.6%)	60 (29.3%)	124 (30.0%)	66 (33.0%)	56 (28.3%)	122 (30.7%)	0.61	0.83	0.83
Chronic renal disease, *n* (%)	14 (6.7%)	7 (3.4%)	21 (5.1%)	24 (12.0%)	21 (10.6%)	45 (11.3%)	0.06	<0.01*	<0.01*
Coronary heart disease, *n* (%)	30 (14.4%)	18 (8.8%)	48 (11.6%)	25 (12.5%)	15 (7.6%)	40 (10.1%)	0.58	0.66	0.48
Other, *n* (%)	86 (41.1%)	77 (37.6%)	163 (39.4%)	77 (38.5%)	58 (29.3%)	135 (33.9%)	0.58	0.08	0.11
Physician type									
Cardigologist, *n* (%)	36 (17.2%)	36 (17.6%)	72 (17.4%)	46 (23.0%)	42 (21.2%)	88 (22.1%)	0.14	0.35	0.09
Primary care physician, *n* (%)	173 (82.8%)	169 (82.4%)	342 (82.6%)	154 (77.0%)	156 (78.8%)	310 (77.9%)			
Free-combination antihypertensives									
ARB, n (%)									
Candesartan				11 (5.5%)	16 (8.1%)	27 (6.8%)			
Irbesartan				16 (8.0%)	20 (10.1%)	36 (9.0%)			
Losartan				40 (20.0%)	59 (29.8%)	99 (24.9%)			
Olmesartan				44 (22.0%)	36 (18.2%)	80 (20.1%)			
Telmisartan				19 (9.5%)	21 (10.6%)	40 (10.1%)			
Valsartan				70 (35.0%)	46 (23.2%)	116 (29.1%)			
CCB, n (%)									
Amlodipine				163 (81.5%)		163 (81.5%)			
Diltiazem				1 (0.5%)		1 (0.5%)			
Felodipine				16 (8.0%)		16 (8.0%)			
Isradipine				3 (1.5%)		3 (1.5%)			
Nicardipine				1 (0.5%)		1 (0.5%)			
Nifedipine				16 (8.0%)		16 (8.0%)			

Abbreviations: SPC = single pill combination; FC = free combination; HCTZ = hydrochlorothiazide; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker.
*$p \leq 0.05$.

BP goal achievement

Overall, 65.9% of patients receiving valsartan-based SPCs and 55.8% patients receiving ARB-based FCs achieved BP goal during a mean observation period (defined as the time period from the 45th day after the index therapy initiation to the BP goal achievement date or a censoring event, whichever came first) of 81 and 90 days, respectively. The unadjusted results from the Kaplan–Meier analyses showed that compared with patients on the ARB-based FC regimens, patients who received valsartan-based SPCs had a significantly higher rate of achieving BP goal over time, beginning from 45 days after the treatment initiation ($p = 0.01$, log-rank test) (Figure 1a). At 1.5 months after the start of BP records (3 months after therapy initiation BP records), the rate of BP goal achievement was 28.9% for ARB FC-treated patients and 31.1% for valsartan SPC-treated patients. At 4.5 months after the start of BP records (6 months after therapy initiation), the corresponding rates were 59.2% and 69.1%, respectively.

Similarly, a higher proportion of patients who were treated with the SPC of valsartan/amlodipine achieved BP goal compared to those treated with FCs of ARB + CCB during the observation period (66.0% during a mean of 81-day observation period vs. 54.0% during a mean of 90-day observation period). The Kaplan–Meier analyses also showed that patients who were treated with the SPC of valsartan/amlodipine had a significantly higher rate of achieving BP goal over time than patients treated with FCs of ARB + CCB ($p = 0.04$), as shown in Figure 1b. At 3 months after treatment initiation, 30.9% patients on valsartan/amlodipine and 29.7% patients on ARB + CCB FCs achieved BP goal. At 6 months, 68.3% patients on valsartan/amlodipine and 59.9% patients on ARB + CCB achieved BP goal.

The descriptive analyses comparing SPC of valsartan/HCTZ vs. FCs of ARB + HCTZ showed similar results. Overall, 65.9% of the patients on valsartan-based SPCs achieved BP goal during a mean of 80-day observation period compared with 57.6% of the patients on ARB-based FCs during a mean of 91-day observation period. The comparison of patients on SPC valsartan/HCTZ vs. patients on ARB + HCTZ using Kaplan–Meier analyses yielded similar trends in favor of the SPC medication, but the difference did not reach statistical significance ($p = 0.07$) (Figure 1c). At 3 months after therapy initiation, 31.2% patients on valsartan/HCTZ and 28.0% patients on ARB + HCTZ FCs were at BP goal. At 6 months, 69.9% and 58.6% patients on these therapies, respectively, achieved BP goal.

After controlling for patient baseline characteristics, physician specialty, and taking into account the physician clustering effect among patients, the multivariate analysis yielded findings consistent with the descriptive analysis. The risk factor estimates derived from Cox proportional hazard models are presented in Tables 2–4. In the comparison between patients on valsartan-based SPC and patients on ARB-based FC therapies, the use of valsartan-based SPCs was independently associated with a higher likelihood of achieving BP goal (hazard ratio [HR]: 1.22, 95% CI: 1.00, 1.49, $p = 0.05$), while being African American and having comorbid diabetes, chronic renal disease, and

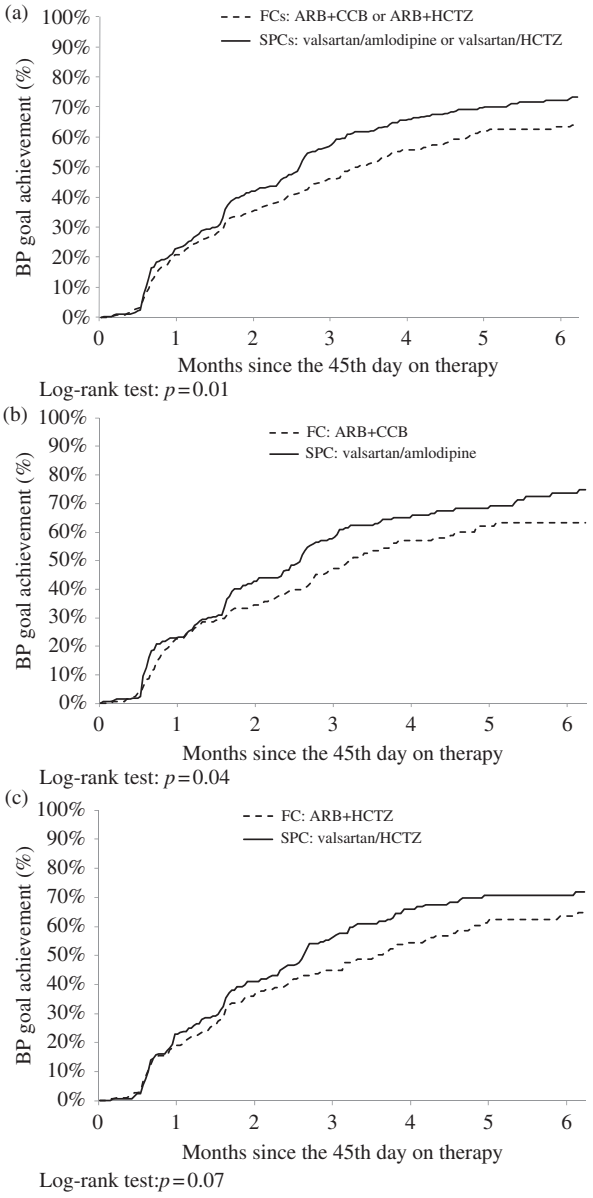

Figure 1. (a) Comparison of blood pressure goal achievement between patients receiving valsartan-based single pill combinations and those receiving angiotensin receptor-blocker-based free combinations. (b) Comparison of blood pressure goal achievement between patients receiving single pill combination of valsartan/amlodipine and those receiving free combination of angiotensin receptor blocker + calcium channel blocker. (c) Comparison of blood pressure goal achievement between patients receiving single-pill combination of valsartan/hydrochlorothiazide and those receiving free combinations of angiotensin receptor blocker + hydrochlorothiazide.

Table 2. Cox proportional hazard model of blood pressure goal achievement comparing patients on valsartan-based single-pill combinations with patients on ARB-based free combinations.

Variable	Estimate	Hazard ratio	95% CI[a]	*P* value
SPC vs. FC	0.199	1.22	(1.00, 1.49)	0.05*
Age (years)	−0.005	1.00	(0.98, 1.01)	0.37
Female	−0.169	0.84	(0.70, 1.02)	0.08
African American vs. non-African American	−0.305	0.74	(0.58, 0.93)	0.01*
HTN ≥ 10 years vs. HTN < 10 years	0.094	1.10	(0.82, 1.48)	0.53
HTN history unknown vs. HTN history known	0.372	1.45	(0.88, 2.39)	0.15
Baseline systolic BP over normal (mmHg)	−0.018	0.98	(0.97, 0.99)	<0.01*
Baseline diastolic BP over normal (mmHg)	−0.004	1.00	(0.98, 1.01)	0.68
Prior use of combination therapy	−0.009	0.99	(0.76, 1.28)	0.95
Concurrent use of other antihypertensives	0.070	1.07	(0.82, 1.40)	0.60
Diabetes	−0.922	0.40	(0.28, 0.56)	<0.01*
Chronic renal disease	−0.458	0.63	(0.41, 0.97)	0.04*
Coronary heart disease	−0.599	0.55	(0.33, 0.93)	0.02*
Other comorbidities	0.060	1.06	(0.80, 1.41)	0.68
Treated by a cardiologist	−0.230	0.79	(0.53, 1.19)	0.27

Abbreviations: CI = confidence interval; SPC = single pill combination; FC = free combination; HTN = hypertension; BP = blood pressure.
Note: total $n = 811$.
[a]Estimated using adjusted covariance matrix that took into account of the clustering effects of physicians, i.e., multiple patients treated by the same physician.
*$p \leq 0.05$.

Table 3. Cox proportional hazard model of blood pressure goal achievement comparing patients on single-pill combination of valsartan/amlodipine with patients on free combinations of ARB + CCB.

Variable	Estimate	Hazard ratio	95% CI	*P* value[a]
Valsartan/amlodipine vs. ARB + CCB	0.231	1.26	(0.91, 1.75)	0.17
Age (years)	−0.006	0.99	(0.98, 1.01)	0.45
Female	−0.099	0.91	(0.68, 1.21)	0.50
African American vs. non-African American	−0.008	0.99	(0.69, 1.42)	0.96
HTN ≥ 10 years vs. HTN < 10 years	−0.035	0.97	(0.65, 1.44)	0.86
HTN history unknown vs. HTN history known	0.681	1.98	(0.95, 4.11)	0.07
Baseline systolic BP over normal (mmHg)	−0.020	0.98	(0.97, 1.00)	<0.01*
Baseline diastolic BP over normal (mmHg)	−0.011	0.99	(0.97, 1.01)	0.39
Prior use of combination therapy	0.002	1.00	(0.72, 1.40)	0.99
Concurrent use of other antihypertensives	0.218	1.24	(0.89, 1.75)	0.21
Diabetes	−1.038	0.35	(0.23, 0.56)	<0.01*
Chronic renal disease	−0.633	0.53	(0.27, 1.04)	0.06
Coronary heart disease	−0.693	0.50	(0.25, 1.00)	0.05*
Other comorbidities	0.139	1.15	(0.81, 1.64)	0.44
Treated by a cardiologist	−0.282	0.75	(0.48, 1.18)	0.22

Abbreviations: ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CI = confidence interval; HTN = hypertension; BP = blood pressure.
Note: total $n = 409$.
[a]Estimated using adjusted covariance matrix that took into account of the clustering effects of physicians, i.e., multiple patients treated by the same physician.
*$p \leq 0.05$.

coronary heart disease were associated with lower likelihood of achieving BP goal (Table 2). When patients on SPC valsartan/amlodipine were compared with patients on FCs of ARB + CCB, the SPC treatment was associated with a higher likelihood of BP goal achievement similar to the overall valsartan SPC group, but the result was not statistically significant (HR: 1.26, 95% CI: 0.91, 1.75, $p = 0.17$). The factors significantly associated with lower goal achievement were having a higher systolic BP above goal at baseline, having diabetes and coronary heart disease. Similarly, the association between the use of SPC valsartan/HCTZ and the likelihood of BP goal attainment was not statistically significant despite the consistent trend (HR: 1.20, 95% CI: 0.94, 1.52, $p = 0.14$). Being African American, having a higher systolic BP above goal at baseline, and having diabetes were significantly associated with lower likelihood of achieving BP goal.

Discussion

This observational study examined the BP goal achievement between patients receiving valsartan-based SPCs vs.

Table 4. Cox proportional hazard model of blood pressure goal achievement comparing patients on single-pill combination of valsartan/HCTZ with patients on free combinations of ARB + HCTZ.

Variable	Estimate	Hazard ratio	95% CI	*P* value[a]
Valsartan/HCTZ vs. ARB + HCTZ	0.179	1.20	(0.94, 1.52)	0.14
Age (years)	−0.004	1.00	(0.98, 1.01)	0.54
Female	−0.192	0.83	(0.65, 1.05)	0.12
African American vs. non-African American	−0.617	0.54	(0.37, 0.78)	<0.01*
HTN ≥ 10 years vs. HTN < 10 years	0.358	1.43	(0.93, 2.19)	0.10
HTN history unknown vs. HTN history known	0.229	1.26	(0.67, 2.37)	0.48
Baseline systolic BP over normal (mm Hg)	−0.016	0.98	(0.97, 1.00)	0.05*
Baseline diastolic BP over normal (mm Hg)	0.005	1.01	(0.98, 1.03)	0.66
Prior use of combination therapy	−0.213	0.81	(0.54, 1.20)	0.29
Concurrent use of other antihypertensives	−0.186	0.83	(0.57, 1.21)	0.33
Diabetes	−0.936	0.39	(0.24, 0.63)	<0.01*
Chronic renal disease	−0.313	0.73	(0.44, 1.22)	0.23
Coronary heart disease	−0.310	0.73	(0.38, 1.41)	0.35
Other comorbidities	−0.084	0.92	(0.64, 1.32)	0.65
Treated by a cardiologist	−0.173	0.84	(0.53, 1.34)	0.47

Abbreviations: HCTZ = hydrochlorothiazide; ARB = angiotensin receptor blocker; HTN = hypertension; BP = blood pressure.
Note: $N = 402$.
[a]Estimated using adjusted covariance matrix that took into account of the clustering effects of physicians, i.e., multiple patients treated by the same physician.
*$p \leq 0.05$.

ARB-based FCs of the same classes using data collected from physician chart review. To our knowledge, this is the first study comparing BP goal achievement between patients receiving valsartan-based SPCs vs. ARB-based FCs in the real-world practice. Valsartan-based SPCs were selected because they were the most commonly prescribed ARB-based SPCs. Based on the analyses of a nation-wide claims database, valsartan/amlodipine accounted for approximately 70% of ARB/CCB SPCs and valsartan/HCTZ accounted for about 38% of ARB/HCTZ SPCs in 2008 (unpublished data). The ARB-based FCs of the same classes were used as the comparison group because these are the real-world FC alternatives to the valsartan-based SPCs. The study focused on the South Central region where higher prevalence rates of cardiovascular diseases and associated mortality, including the prevalence of hypertension and hypertension-related mortality, are observed. The results showed that patients who were initiated on or switched to valsartan-based SPC antihypertensive therapies had a higher likelihood of achieving BP goal during the observation period compared with patients who were given FCs of ARB + CCB or ARB + HCTZ. Kaplan–Meier analysis showed a consistent advantage in favor of the valsartan-based SPC medications in BP goal achievement over time. After adjusting for baseline characteristics in the multivariate regression analysis, the comparison between patients on either of the valsartan-based SPCs and patients on any of the ARB-based FC regimens showed that SPC use was associated with significantly higher likelihood of BP goal achievement. In both subgroup comparisons, the HRs suggested that the trends consistently favored valsartan SPCs, but the comparison was not statistically significant relative to ARB FC regimens. The non-significant results could be due to lack of real difference between the comparison treatments or the small sample size in these subgroups. In addition to the main findings, the study also identified risk factors that are associated with lower rate of BP goal achievement, such as being African American, having a higher systolic BP over the goal, and having comorbid diabetes.

Although previous studies have consistently established the effect of SPC vs. FCs on improving patient compliance at the national and state level[9–13,15,16], there is a paucity of evidence on whether this advantage can translate into clinical outcomes, such as BP goal achievement. A retrospective study of 13 managed care organizations demonstrated that patients with high level of compliance with antihypertensive treatment were more likely to achieve BP control than patients with medium or low levels of compliance[18]. However, the study was focused on monotherapies and thus the findings may not be extrapolated to the comparison of SPC vs. FC therapies.

Nevertheless, recent clinical trials did support the advantage of SPC therapies over FC therapies in BP control. A recent meta-analysis found that the use of an SPC antihypertensive drug was associated with an additional 4.1 mmHg reduction in systolic pressure and 3.1 mmHg reduction in diastolic pressure compared with FC therapies though the differences did not reach statistical significance[12]. Two other clinical trials have also suggested that SPCs are more effective in BP control. Mancia *et al.*[24] showed that patients treated with SPC candesartan cilexetil/HCTZ had a higher rate of BP goal achievement compared with patients who received FCs of a previously prescribed antihypertensive monotherapy plus HCTZ.

In another study by Schweizer and colleagues[25], 138 patients who failed to achieve diastolic BP goal after 4 weeks of FC treatment with 32 mg of candesartan and 25 mg HCTZ and were switched to SPC of valsartan 160 mg/HCTZ 25 mg were able to achieve significant BP reduction after receiving the SPC. These results are in contrast with the findings from earlier clinical trials (mostly in the 1980s), which showed no significant difference between SPC and FC in BP outcomes[19,21–23]. However, antihypertensive treatments have changed dramatically since the 1980s. The discrepancies between the earlier and later clinical trials may be explained by different drugs and evolvement of hypertension treatment, e.g., availability of additional combination therapies and adaptation of increasingly more aggressive treatment paradigms.

There are major differences between the controlled conditions in clinical trials and real-world clinical practice. Patients who participate in clinical trials may be more likely to comply with assigned treatments regardless of the number of pills, but patients in real-world settings may be more affected by the complexity of medication regimens and increasing medical costs and thus present a larger difference in compliance and possibly outcome between SPC and FC regimens. Therefore, there is an increasing need for real-world clinical evidence on the effectiveness of SPCs vs. FCs. Using the real-world data, the current study further supported that patients receiving SPCs were more likely to achieve BP goal compared to those receiving FCs. Future studies may further examine how this difference in BP goal achievement translates into reduction in risk of cardiovascular events.

In addition, the study also showed that higher systolic BP above the normal cut-off and comorbid diabetes were both independently risk factors associated with lower likelihood of achieving BP goal in both the overall and subgroup analyses, which suggests that these patients should be prioritized for antihypertensive aggressive therapy. However, this study was not powered to examine whether SPCs had better benefits in these difficult-to-treat subgroups. Further observational studies are needed to examine whether valsartan-based SPCs would have more beneficial effect compared to ARB-based FCs in the presence of comorbidities or polypharmacy as they increase the treatment and compliance burden for patients.

The study has several limitations. First, patients were not randomized to either valsartan-based SPC or ARB-based FC treatments, and unobserved differences may have influenced the results. However, in the multivariate analyses, key factors that may have affected BP goal achievement, such as demographics, comorbidities, history of hypertension, other anti-hypertensive medications, etc., were controlled to examine the independent association between valsartan-based SPCs vs. ARB-based FCs. The results were consistent with the findings from the descriptive analyses. To the extent that the unobserved factors associated with BP goal achievement do not affect the choice of valsartan-based SPCs vs. ARB-based FCs, the results from this study would be valid. Further, the study findings may have limited generalizability. The study was conducted in the South Central region and thus the results may not apply to other regions as the practice pattern may vary. The generalizability of the findings may be further limited if patients from physicians who responded have different characteristics from those who did not respond. However, efforts were made to randomly recruit physicians and patients to ensure the sample was representative of adult patients receiving the index therapies in the South Central region. In addition, the BP measures were collected starting at 45 days after the initiation of the index therapy because the guidelines recommend that hypertensive patients should be followed up monthly. Therefore, the study could not identify BP goal achievement before the 45th day after index therapy initiation; nor could it examine how fast patients achieved BP goal in the valsartan SPC group vs. the ARB FC group. Lastly, BP goal achievement in the real world can be a function of efficacy and compliance. While the current study estimated the overall difference in BP goal achievement between valsartan SPCs vs. ARB FCs, it was not able to differentiate how much of the overall difference was attributable to the differences in compliance, efficacy or safety.

It is worth noting that by including different ARB-based FCs in the comparison group, the differences between the SPC vs. FC groups in this study could result from different forms (SPC vs. FC), different ingredients (valsartan vs. a combination of ARBs or amlodipine vs. a combination of CCBs) or different doses of the same ingredients. The study was not intended to focus exclusively on the effect resulting from different forms of drugs. By comparing valsartan-based SPCs vs. the broad category of ARB-based FCs, the study was better tailored to real-world decision making. However, future studies can be designed to separately estimate the effects on BP goal achievement resulting from different forms or different ingredients.

Also of note, the study used the BP goal definition suggested by the guidelines from JNC7 and the American Heart Association/American College of Cardiology[1–2]. The guidelines have been evolving toward more strict control of hypertension; so will be the definition of BP goal. These changes may be reflected in JNC8. Nevertheless, we do not expect that the changes in BP goal definition would affect our conclusion.

Conclusions

Hypertensive patients who were treated with valsartan-based SPCs were significantly more likely to achieve BP

goal compared with patients who were treated with FC regimens of ARB + CCB and ARB + HCTZ in the real-world clinical practice in the South Central region. The significance was achieved at two-sided $\alpha = 0.05$.

Transparency

Declaration of funding

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Declaration of financial/other relationships

J.C., W.Y., K.H.K., T.F. and J.O. have disclosed that they are employees of Novartis. J.X., M.T., A.P.Y., and E.Q.W. have disclosed that they are employees of Analysis Group, Boston, MA, USA which received funding for this study.

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