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Efficacy and safety of single pill combination of amlodipine and valsartan in hypertensive Saudi patients

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Abstract. – OBJECTIVE: A significant global health issue that affects 25.5% of Saudi people is hypertension (HTN). According to international recommendations, most HTN patients require more than one therapy to reach their blood pressure targets (BP). Therefore, it would be preferable to utilize two medications from distinct classes separately or in a predetermined combination. According to recent studies, a single-pill combination (SPC) may be more efficient. This study evaluated the safety and tolerability of Amlodipine/Valsartan (Aml/Val) SPC in Saudi hypertensive patients, as well as the effectiveness of the medication.

PATIENTS AND METHODS: Observational research was done prospectively at the King Fahad Armed Forces Hospital in Jeddah, Saudi Arabia. The effectiveness of the treatment and the percentage of 159 hypertensive patients who achieved the target blood pressure values (140/90; 130/80 mmHg) among those with diabetes mellitus (DM), chronic kidney disease (CKD), other cardiovascular disorders, and responders were assessed from the beginning to the endpoint (week 23).

RESULTS: According to the results, taking Aml/Val SPC significantly lowered all patients' baseline systolic and diastolic blood pressure readings by -17.97 and 8.58 mmHg, respectively. 43.4% of patients successfully met their BP therapeutic objectives by bringing their blood pressure levels back to normal, including 51.4% of patients under 65, 39.3% of patients with chronic kidney disease, and 26.2% of diabetic patients. Aml/Val 10/160 mg significantly lowers SBP, more than Aml/Val 5/160 mg (-13.32% vs. -9.00%, $p<0.050$). Vertigo (6.30%), respiratory tract infections (4.0%), and ankle edema (2.50%) were the most frequent adverse events.

CONCLUSIONS: Aml/Val SPC therapy effectively lowered BP and had few side effects while being well-tolerated in people with hypertension.

Key Words:
Amlodipine, Valsartan, Hypertensive, Patients.

Introduction

A significant issue for global health is hypertension (HTN), whose prevalence is expected to rise from 972 million in 2000 to 1.56 billion by 2025[1]. Functional, structural, and vascular problems associated with HTN harm the heart, vasculature, brain, kidneys, and other body organs and cause early morbidity and mortality[2]. HTN was responsible for 13.5% of all premature deaths (about 7.6 million), 54% of strokes, and 47% of ischemic heart diseases[3]. For many Saudis, hypertension in Saudi Arabia (SA) has become a growing health concern, necessitating early testing and early detection through screening services[4]. According to the Saudi National Health Survey from 2013, 78.9% of individuals with high blood pressure (BP) kept track of the drugs they took. Nearly 45% of patients on HTN medicines had their blood pressure under control. However, out of all hypertensive people, 57.8% were not diagnosed, 20.2% had treatment but it wasn't controlled, 16.6% had treatment, but it was controlled, and 5.4% had no treatment[5].

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Cardiovascular problems and organ damage are avoided when blood pressure is lowered with antihypertensive medications (CVDs). Antihypertensive medication has been available for many years thanks to the discovery of numerous pharmacological classes. First-line antihypertensive medications include angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs), beta-blockers (BBs), and thiazide diuretic therapy. These drugs are particularly effective in lowering blood pressure and preventing CVD[6].

Although CCBs were first used in coronary heart disease (CHD) more than thirty-five years ago, their effectiveness with HTN quickly made them the norm. The initial symptoms of HTN were accompanied by angina, peripheral vascular disease, and specific arrhythmias[7]. Amlodipine (Aml) is a long-acting lipophilic generation dihydropyridine (DHP) CCB. It reduces vascular resistance by preventing calcium from entering smooth muscle cells, cardiomyocytes, and blood vessels[8]. First-line ARBs for treating hypertension are effective and well-tolerated, although they frequently need to be combined with other drugs to achieve the objectives[9]. The Valsartan Long-Term Use Evaluation (VALUE) demonstrated that valsartan (Val) medication is more effective compared with Aml at reducing cardiac endpoints in patients with high risks of hypertension[10].

According to international recommendations, most hypertension patients need more than one drug to get their blood pressure target. Therefore, combining two separate groups of free or fixed medications is preferable[11]. The majority of guidelines encourage the use of single-pill combinations (SPC)[9,12]. Combining CCBs and ARBs is one of the selected options. Patients who use other antihypertensive medications in monotherapy may find Aml/Val SPC more effective[13,14].

As a result, this research sought to assess the effectiveness of Aml/Val SPC as an antihypertensive treatment in Saudi patients complaining of essential hypertension as well, as the safety and tolerability of the medication.

Patients and Methods

Study Design

This non-interventional, prospective, observational research aims to investigate how a drug functions in a real-world setting.

Setting

The King Fahad Armed Forces Hospital (KFAFH) in Jeddah, Saudi Arabia, hosted the current study from 2018 to 2019 (238 weeks). Patients' consent was taken at hospital admission to use their data with complete confidentiality. The study protocol was designed following the Declaration of Helsinki and approved by KFAFH Researchers Ethics Committee (REC# 262).

Inclusion Criteria

A single pill containing the antihypertensive medications Amlodipine 5/10 mg and Valsartan 160 mg once time daily was provided to Saudi female and male adults >18 years who had hypertension. Patients with uncontrolled hypertension and albuminuria (urinary albumin: creatinine ratio (UA/CR) > 3.5 mg/ mmol), as well as those with diabetes mellitus (DM), other cardiovascular diseases (CVDs), and chronic kidney disorders (CKD), were also included.

Exclusion Criteria

Patients under 18, non-Saudis, and females who were pregnant, planning a pregnancy, or nursing were ineligible for the study. Patients were also disqualified if they had a history of Aml/Val or any of the formulation's excipients hypersensitivity. Patients whose Aml/Val dosage increased or who received another antihypertensive drug (apart from thiazide diuretic) during the trial were excluded.

Patients' Data

All pertinent patient information was gathered and documented from patient files and digital information systems, including demographic information (such as age and gender). In addition, systolic (SBP) and diastolic (DBP) blood pressure, hypertension stage (stage 1 or stage 2), associated comorbidity (DM, CKD, other CVD as coronary artery diseases, and heart failure), biochemical analysis, use of other antihypertensive medications (BB, ARBs, ACEs, CCBs, diuretics), dosing regimen, sampling time, and side effects are all taken into consideration (vertigo, ankle edema, respiratory tract infections).

Dosing Regimen of Exforge

After that, the patient was prescribed single-pill combination medication (Aml/Val SPC) at doses of either 10/160 or 5/160 mg once daily. After that, the doctors decided to up or down the dosage, add or not add another antihypertensive drug.

Study Population

One hundred fifty-nine hypertension individuals who received Aml/Val SPC 5/160 or 10/160 mg treatments were involved in the study. Throughout the entire observation period, every patient visited the doctor three times.

Study Procedures

At least three exams were performed at the baseline, fourth, thirteenth, and study endpoint weeks. Detailed data from all these exams were documented. There was no washout period available to generate baseline blood pressure values in the recruited patients, so the dose of Aml/Val SPC 5/160mg and 10/160mg as recommended by the treating physician was reported at baseline. Therefore, baseline blood pressure readings are those taken at the first visit, and in many patients, they reflect the level of blood pressure that was reached while taking previous antihypertensive medication. At the fourth- and thirteenth weeks visits, the investigators were also questioned for medication compliance.

Effectiveness Assessments

Antihypertensive efficacy

SBP and DBP change from the beginning of the study until its conclusion (the 23rd week) were noted. In addition, the percentage of patients getting therapeutic BP goals (140/90; 130/80 mmHg in patients with DM and CKD) and BP response [SBP 140 mmHg (130 mmHg for patients with diabetes and chronic kidney disease) or a reduction of 20 mmHg; DBP 90 mmHg (80 mmHg for patients with DM and CKD) or a reduction of 10 mmHg] SBP and DBP changes in patients subgroups (including age 65 years and older, gender, DM, CKD, stages of hypertension 1 and 2) from baseline to week 23 were noted.

Control and response rate

The percentage of patients who were responders and reached target BP (140/90 mmHg for non-diabetics or 130/80 mmHg for DM and CKD). A reduction of 20 mmHg, DBP of 90 mmHg (80 mmHg for patients with DM and CKD), or a reduction of 10 mmHg) was achieved by a significant number of the patients who responded. With the aid of spot urine albumin creatinine ratio (UA/CR), the anti-albumin urea impact of amlodipine and valsartan SPC was shown in CKD patients.

Safety Assessment

Safety evaluation of drug side effects

The incidence of ankle edema, vertigo, and respiratory tract infections with and without a causal relationship to the utilization of Aml/Val together was examined to assess safety.

Safety and tolerability assessments of included laboratory evaluations

The following routine blood tests were performed for hypertension patients in a clinic following the hospital protocol and based upon JNC 8 protocol irrespective to suspected relation to study medication. Safety and tolerability evaluation in the form of Mean/Median alteration from baseline to endpoint, including the following tests: Blood urea nitrogen (reference range: 7-24 mg/dL), sodium (reference range: 135-145 mmol/L), vitamin D (reference range: >30 ng/ml), calcium (reference range: 2.2-2.7 mmol/L), albumin (reference range: 37-50 g/L), hemoglobin (reference range: 14-18 g/dL), and potassium (reference range: 3.5-5.0 mmol/L).

Statistical Analysis

The data entry was done on an Excel document. Before performing any statistical analyses, the data was cleansed. The IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA), was used to analyze the data, which were shown as number (%) or mean +/- standard deviation (SD) as necessary. The Shapiro-Wilk test was employed to assess the normality of the data distribution. In addition, the paired *t*-test, Person Chi-square test, and Mann-Whitney test were used as necessary for inferential statistics (i.e., testing for significance). If the *p*-values were < 0.05, the findings were deemed statistically significant.

Results

The patients' ages ranged from 33 to 90, with a mean age of 56.05. Most patients (78.0%) and males (75.5%) belonged to the 65+ age group. DM (38.4%), CKD (35.2%), and other CVDs (such as atherosclerosis, infarction, myocardial ischemia, and coronary artery disorders) (8.8%) were associated with comorbidities. Stage 2 was more common than stage 1 in the hypertensive stage (89.9% *vs.* 10.1%). Aml/Val 10/160 mg was the strength

Table I. Demographics and clinical data of all participants (n=159).

Characteristics	Value
Age (years)	56.05±11.14
Age groups	
< 65 years	124 (78.0%)
≥ 65 years	35 (22.0%)
Gender	
Male	120 (75.5%)
Female	39 (24.5%)
Comorbidity	
Diabetes mellitus	61 (38.4%)
Chronic renal diseases	56 (35.2%)
Other cardiovascular disorders	14 (8.8%)
Hypertensive stage	
Stage 1	16 (10.1%)
Stage 2	143 (89.9%)
Dosing regimen	
Aml/Val 5/160 mg	65 (40.9%)
Aml/Val 10/160 mg	94 (59.1%)
Previous antihypertensive therapy	
Diuretics	94 (59.1%)
Calcium channel blockers (CCBs)	88 (55.3%)
Angiotensin converting enzyme inhibitors (ACEI)	71 (44.7%)
Angiotensin II receptors blockers (ARBs)	65 (40.9%)
Beta blockers (BBs)	45 (28.3%)

that most of the patients utilized (59.1% *vs.* 40.9%). Diuretics (59.1%), ACEI (44.7%), CCBs (55.3%), ARBs (40.9%), and BBs (28.3%) were the previous hypertension treatments used (Table I).

Tables II and III provide an overview of the variations in SBP and DBP (pre-Aml/Val SPC therapy baseline - post-treatment). The changes in SBP and DBP were respectively -17.97±14.19 and -8.58±12.47 mmHg for all subjects. Patients who used Aml/Val 10/160 mg had considerably lower SBP changes than those who used Aml/Val 5/160 mg (-20.98±13.26 against -13.60±14.46, p=0.050); patients with CKD had significantly lower changes than those without CKD (-22.71±12.78 compared to -15.39±14.32, p=0.050) (Table II).

When comparing DM patients to non-DM patients, non-CKD patients to CKD patients, stage 2 hypertension patients to stage 1 hypertensive patient, and DM patients to non-DM patients, the change in DBP were considerably reduced 11.70±14.50 against -6.63±10.64, p=0.050) (Table III).

Table IV displays the average blood pressure readings for all patients at the baseline, fourth, thirteenth, and twenty-third weeks of the study, and at baseline, two months prior to the start of Aml/Val SPC administration, and one month prior. The information showed that both SBP and DBP decreased over time.

Table II. Changes in systolic blood pressure (SBP) before and after Aml/Val SPC usage.

Variable	SBP before	SBP after	Changes SBP	% of Change	Significance
Patients (n=159)	154.87±12.47	136.90±11.74	-17.97±14.19	-11.22%	
Age groups					
< 65 years (n=124)	155.45±12.17	136.75±11.35	-18.70±14.07	-12.03%	0.221
≥ 65 years (n=35)	152.82±13.46	137.45±13.17	-15.37±14.54	-10.01%	
Gender					
Male (n= 120)	152.85±11.44	135.10±10.82	-17.75±14.82	-11.61%	0.744
Female (n= 39)	161.07±13.60	142.46±12.81	-18.61±12.20	-11.55%	
Dosing regimen					
Aml/Val 5/160 mg (n=65)	151.07±10.05	137.46±11.35	-13.60±14.46	-9.00%	**0.050***
Aml/Val 10/160 mg (n=94)	157.50±13.33	136.52±12.05	-20.98±13.26	-13.32%	
Diabetic mellitus					
Yes (n=61)	152.58±11.49	136.66±12.05	-15.92±16.45	-10.43%	0.151
No (n=98)	156.30±12.90	137.06±11.60	-19.24±12.51	-12.31%	
Chronic renal diseases					
Yes (n=61)	159.60±12.87	136.89±12.02	-22.71±12.78	-14.22%	**0.050***
No (n=98)	152.30±11.52	136.91±11.64	-15.39±14.32	-10.11%	
Cardiovascular disorders					
Yes (n=14)	158.14±10.58	140.57±12.96	- 17.57±6.93	-11.11%	0.914
No (n=145)	154.55±12.63	136.55±11.60	-18.00±14.72	-11.65%	
Hypertensive stage					
Stage 1 (n=16)	152.58±15.16	136.98±11.65	-15.60±16.55	-10.22%	0.484
Stage 2 (n=143)	155.13±12.17	136.90±11.79	-18.23±13.95	-11.75%	

Table III. Changes in diastolic blood pressure (DBP) before and after Aml/Val SPC administration.

Variable	DBP before	DBP after	Changes DBP	% of Change	Significance
Patients (n=159)	87.30±13.23	78.72±9.94	-8.58±12.47	-9.83%	-
Age groups					
< 65 years (n=124)	88.24±13.90	79.23±10.34	-9.01±13.11	-10.21%	0.667
≥ 65 years (n=35)	83.96±10.00	76.90±8.29	-7.06±9.86	-8.41%	
Gender					
Male (n= 120)	87.98±13.08	78.92±9.77	-9.06±12.92	-10.30%	0.394
Female (n= 39)	85.18±13.66	78.08±10.56	-7.09±10.99	-8.32%	
Dosing regimen					
Aml/Val 5/160 mg (n=65)	90.33±14.60	79.62±8.32	-10.72±13.86	-11.87%	0.722
Aml/Val 10/160 mg (n=94)	85.19±11.83	78.09±10.93	-7.10±11.25	-8.33%	
Diabetic mellitus					
Yes (n=61)	91.31±15.28	79.60±7.45	- 11.70±14.50	-12.81%	**0.050***
No (n=98)	84.80±11.15	78.17±11.22	- 6.63±10.64	-7.82%	
Chronic renal diseases					
Yes (n=61)	83.42±11.45	78.16±11.97	- 5.26±11.38	-6.31%	**0.050***
No (n=98)	89.40±13.71	79.02±8.70	-10.38±12.72	-11.61%	
Cardiovascular disorders					
Yes (n=14)	86.90±11.89	78.69±10.78	- 8.21±8.98	-9.45%	0.909
No (n=145)	87.33±13.39	78.72±9.90	- 8.61±12.78	-9.86%	
Hypertensive stage					
Stage 1 (n=16)	86.24±11.44	78.55±9.57	-7.69±11.69	-8.92%	**0.050***
Stage 2 (n=143)	96.68±22.38	80.19±13.13	-16.51±16.41	-17.08%	

Patients in the age groupings of <65 years and ≥65 years had insignificant differences in either SBP or DBP at baseline and three times (Figure 1).

The proportion of patients who achieved either SBP, DBP or both DBP and SBP goals (<140/90 mmHg, and/or <130/80 mmHg for DM and CKD) in all patients were (36.5%, 73.0%, 33.3%), in patients with CVDs (14.3%, 71.4%, 4.3%), DM (16.4%, 57.4%, 11.5%), CKDs (30.4%, 76.8%, 28.6%), hypertensive (stage 1) (37.5%, 62.5%, 31.2%) and hypertensive (stage 2) (36.4%, 74.1%, 33.6%), age subgroups <65 years (33.9%, 71.0%, 29.8%), age ≥ 65 years (45.7%, 80.0%, 45.7%), male (41.7%, 71.7%, 37.5%), female (20.5%, 76.9%, 20.5%), Aml/Val SPC 5/160 mg (34.0%, 72.3%, 36.9%) and Aml/Val SPC 5/160 mg (40.0%, 73.4%, 30.9%) (Table V).

The proportion of cases who get either SBP (≥20 mmHg), DBP (≥10 mmHg), or both SBP and DBP targets in all patients were (39.0%, 40.9%, 18.2%), in patients with CVDs (42.9%, 35.7%, 28.6%), DM (36.1%, 42.6%, 21.3%), CKDs (51.8%, 33.9%, 17.9%), hypertensive (stage 1) (31.2%, 56.2%, 18.8%) and hypertensive (stage 2) (39.9%, 39.2%, 18.2%), age subgroups <65 years (41.1%, 41.9%, 18.5%), age ≥ 65 years (31.4%, 37.1%, 17.1%), male (40.8%, 43.3%, 21.7%), female (33.3%, 33.3%, 7.7%), Aml/Val SPC 5/160mg (30.8%, 49.2%, 16.9%) and Aml/Val SPC 5/160 mg (44.7%, 35.1%, 19.1%) (Table VI).

In all patients who followed Aml/Val SPC side effects were vertigo (6.3%) followed by respiratory tract infections (4.4%) and ankle edema (2.5%) (Figure 2).

There were insignificant changes between Post- and Pre-Aml/Val SPC usage of serum values of creatinine, blood urea nitrogen, albumin, and potassium (Table VII).

Table IV. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) among patients at six time points of study.

Time	SBP	DBP
2 months before	151.14±12.56	85.64±11.12
Month before	154.14±17.61	85.29±14.61
Baseline	155.59±15.82	88.69±20.28
4th week	134.27±12.71	74.10±9.90
13th week	135.19±12.95	76.87±7.03
23rd week	127.20±15.29	76.65±10.04

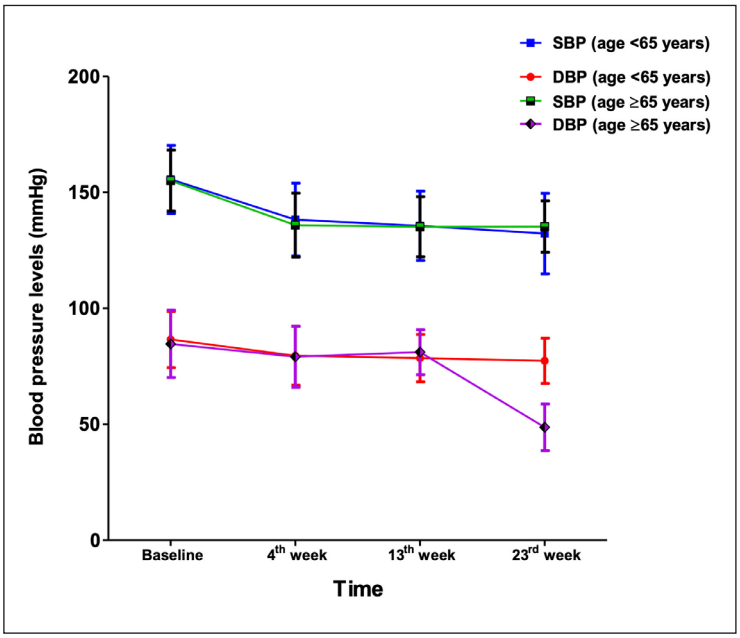

Figure 1. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) among age subgroups of patients at four-time points of study.

Table V. Proportion of patients achieved blood pressure goal (<140/90 mmHg, and / or <130/80 mmHg for DM & CKD) based upon associated comorbidity, demographic characteristics, and dose of Aml/Val SPC.

Response	SBP	DBP	Both SBP and DBP
All participants (n=159)	36.5%	73.0%	33.3%
CVD (n=14)	14.3%	71.4%	4.3%
DM (n=61)	16.4%	57.4%	11.5%
CKD (n=56)	30.4%	76.8%	28.6%
HTN stage 1 (n=16)	37.5%	62.5%	31.2%
HTN stage 2 (n=143)	36.4%	74.1%	33.6%
< 65 years (n=124)	33.9%	71.0%	29.8%
≥ 65 years (n=35)	45.7%	80.0%	45.7%
Male (n=120)	41.7%	71.7%	37.5%
Female (n=39)	20.5%	76.9%	20.5%
Aml/Val 5/160 mg (n=65)	34.0%	72.3%	36.9%
Aml/Val 10/160 mg (n=94)	40.0%	73.4%	30.9%

CVD: cardiovascular diseases; DM: diabetes mellitus; CKD: chronic kidney diseases; HTN: hypertension.

In 56 patients with CKDs, the urinary albumin/creatinine ratio (UA/CR) and hemoglobin levels were estimated. Kidney impairment resulted in a defect in the UA/CR due to a defect in glomerular filtration and a defect in the hemoglobin level due to a defect in the level of the erythropoietin hormone that is secreted by the kidney. UA/CR levels significantly decreased in Post-Aml/Val SPC administration compared to Pre- Aml/Val SPC usage (4.32±1.94 against 5.23±1.68 mg/mol, p=0.050). However, hemoglobin levels between Post- and Pre-Aml/Val SPC consumption did not differ significantly (13.98±1.68 *vs.* 13.79±1.53 g/dl, p = 0.224) (Figure 3).

In 103 patients without CKDs, serum calcium and vitamin D levels were assessed. Compared to when Aml/Val SPC was not used, the serum vitamin D level was considerably higher (57.36±19.98 *vs.* 44.69±14.16 nmol/L, p=0.050). However, between the use of Post-Aml/Val SPC and Pre-Aml/Val SPC, there were minor changes in serum calcium (2.64±0.50 *vs.* 2.79±2.60 mmol/L, p=0.551) (Figure 4).

Table VI. Proportion of patients' response by reduction of SBP to ≥20 and/ or DBP to ≥ 10 mmHg based upon associated comorbidity, demographic characteristic, and dose of Aml/Val SPC.

Response	SBP (≥ 20 mmHg)	DBP (≥ 10 mmHg)	Both SBP and DBP
All participants (n=159)	39.0%	40.9%	18.2%
CVD (n=14)	42.9%	35.7%	28.6%
DM (n=61)	36.1%	42.6%	21.3%
CKD (n=56)	51.8%	33.9%	17.9%
HTN stage 1 (n=16)	31.2%	56.2%	18.8%
HTN stage 2 (n=143)	39.9%	39.2%	18.2%
< 65 years (n=124)	41.1%	41.9%	18.5%
≥ 65 years (n=35)	31.4%	37.1%	17.1%
Male (n=120)	40.8%	43.3%	21.7%
Female (n=39)	33.3%	33.3%	7.7%
Aml/Val 5/160 mg (n=65)	30.8%	49.2%	16.9%
Aml/Val 10/160 mg (n=94)	44.7%	35.1%	19.1%
Aml/Val 10/160 mg (n=94)	40.0%	73.4%	30.9%

CVD: cardiovascular diseases; DM: diabetes mellitus; CKD: chronic kidney diseases; HTN: hypertension.

Figure 2. Side effects after Aml/Val SPC intake in all patients (n=159).

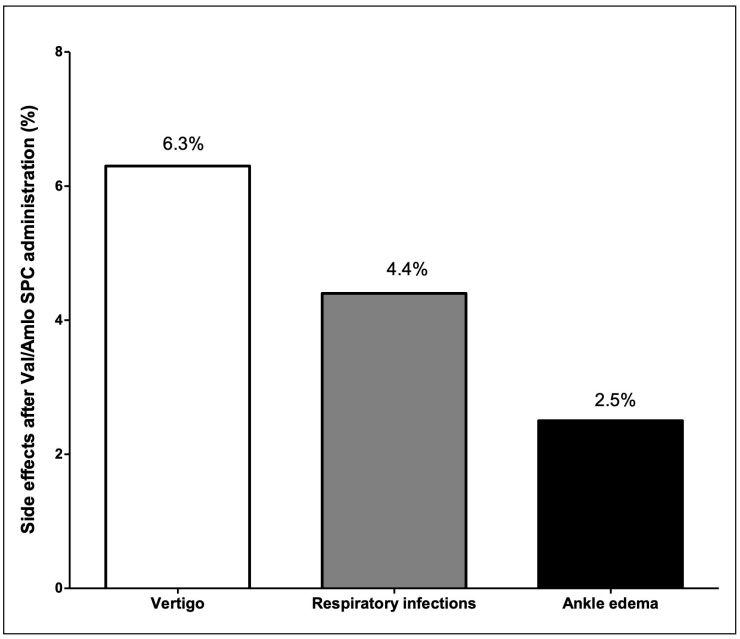

Table VII. Measured laboratory parameters pre and post Val/Amlo SPC usage (n=159).

Variable	Reference range	Pre- usage	Post- usage	Significance
Creatinine (umol/L)	50-98	80.86±18.58	78.57±15.57	0.062
BUN (mmol/L)	2.1-6.4	5.29±1.41	5.41±1.67	0.334
Albumin (g/L)	37-50	43.58±3.26	43.44±4.08	0.687
Potassium (mmol/L)	3.5-5.1	4.15±0.72	4.29±1.01	0.107

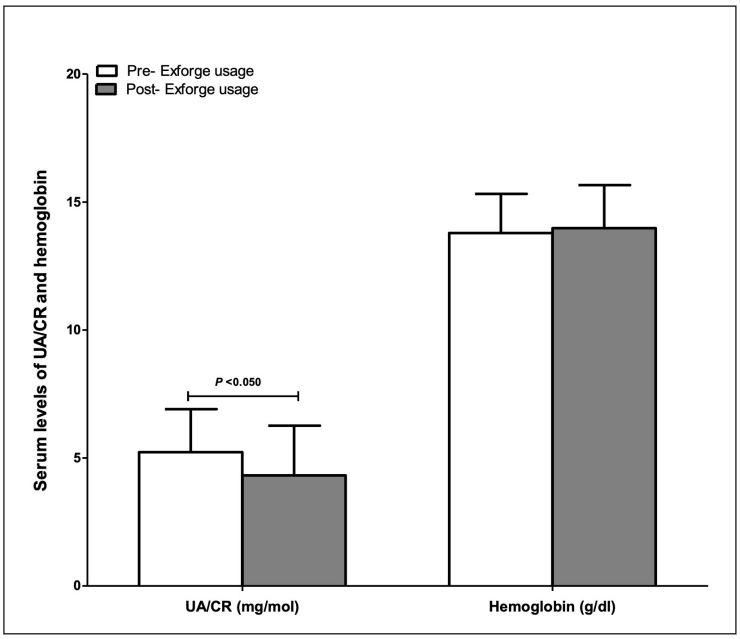

Figure 3. UA/CR and hemoglobin levels before and after Aml/Val SPC administration in patients with chronic kidney diseases (n=56).

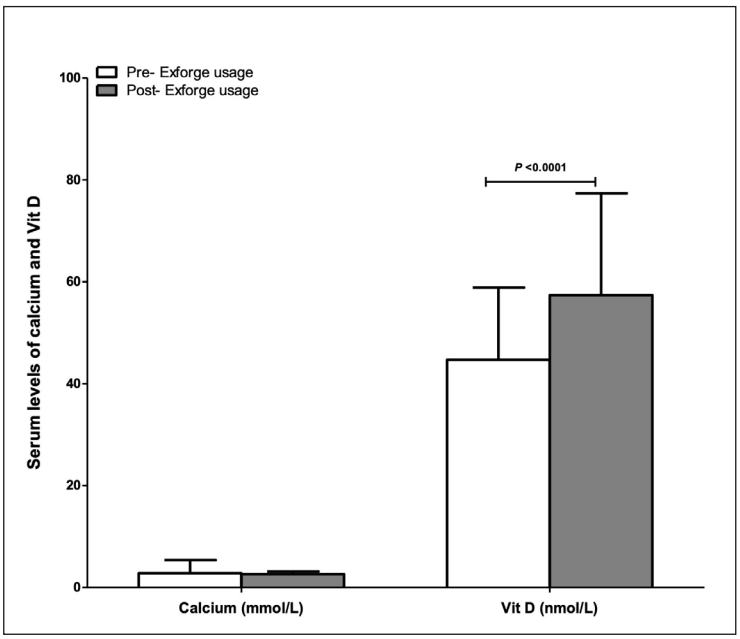

Figure 4. Serum levels of calcium and vitamin D before and after Aml/Val SPC administration in all patients except patients with chronic kidney diseases (n=103).

Discussion

Hypertension has enormous effects on community health. HTN is common in the entire world. However, real-world data about Aml/Val SPC's safety and effectiveness in HTN are limited[15]. The safety and effectiveness of the combination Aml/Val SPC in Saudi hypertensive patients are assessed in this study for the first time by non-interventional surveillance in Saudi Arabia. According to the study, men were more likely than women to have HTN (75.5% *vs.* 24.5%). The average age of hypertensive patients was 56.05 years; approximately 78.5% and 21.5% were <65 and ≥65 years. Other researchers found the same observations for elevated HTN risk with older age and in men in Saudi Arabia[5,16]. In 10,735 Saudis aged ≥15 years, El Bcheraoui et al[5] found that DBP and SBP were hypertension or borderline in 15.2% and 40.6%. They found that males with old age, obesity, T2DM, and

hypercholesterolemia were at elevated risk of getting HTN. About 27.2% of individuals >30 years of age were hypertensive. According to research by Alhawari et al[16], university students were diagnosed with systolic hypertension in 17.8% of cases (SBP > 130 mmHg) compared to 6.1% in cases where SBP > 140 mmHg was used, and DBP hypertension in 45.4% of cases (DBP > 80 mmHg) as opposed to 10.5% in cases where DBP > 90 mmHg was used[16].

Patients with HTN could experience several long-term problems. Comorbidities among HTN Saudi patients in this study were DM (38.4%), CKD (35.2%), and other CVDs (8.8%). Alshaya et al[17] revealed that about 75% of adults with DM had hypertension. According to research by Noh et al[18], comorbidity was prevalent in Korean hypertensive cases. According to their findings, those with HTN were 2.37 times more likely to have diabetes than people without HTN (14.7% *vs.* 6.2%). Additionally, patients with hypertension had a higher frequency of other CVDs (3.6%).

Stage 2 HTN was the most common diagnosis among patients in the current study (89.9%). Additionally, diuretics were used more frequently to treat hypertension (59.1%) than CCBs (55.3%), ACEI (44.7%), ARBs (40.9%), and BB (28.3%). The results of this research were the same as others[11,19]. Assaad-Khalil and Nashaat[19], however, establish that the majority of HTN patients (78.9%) were using antihypertensives prior to the research, with ACEIs (20.8%), selective BB (24.5%), CCBs (15.0%), and ARBs (10.6%) being the most specialized antihypertensive categories. Cooper-DeHoff and Pepine[20] conducted case-control research with 353 cases and 952 controls to examine the efficacy of managed care for individuals with low-risk hypertension. The focus of the study was on diuretic antihypertensive regimens that included a renin-angiotensin-blocker, or CCB, in addition to the diuretic. Long-acting CCB is strongly advised to maintain BP control and reduce CVD morbidity and mortality in low- and high-risk populations, including older persons and those with diabetes[20].

In the Saudi capital Riyadh, in order to establish the degree of HTN regulation and the most often prescribed drugs among hypertension patients visiting a primary health center, Siddiqui et al[21] conducted a cross-sectional study. Among the 108 hypertension patients studied, 51% of females and 35% of males took only one prescription. Drugs including ACEI (35%), CCBs (17.5%), and BB (14%) were most frequently utilized. They concluded that BP control in hypertension individuals using medication was still significantly below most recommendations.

An appropriate therapeutic strategy for preventing peripheral edema associated with amlodipine would be a potent and highly selective blocker of the renin-angiotensin pathway, including Valsartan for arteriolar dilation of amlodipine. Peripheral edema is brought on by venule dilatation and fluid leakage in the tissue. So, two effective mechanisms (renin-angiotensin pathway blockers and calcium antagonists) are intended to quickly and effectively regulate blood pressure, with combos of amlodipine and valsartan significantly improving BP reduction and having a higher sensitivity than amlodipine alone[22,23]. According to the current investigation findings, Aml/Val SPC usage significantly lowers both SBP and DBP in all patients. Additionally, after receiving Aml/Val SPC treatment, SBP in men was much lower than in women. Additionally, both the levels of SBP and DBP were significantly lower after Aml/Val SPC treatment than before. The findings of this research are similar to other research[24,25] in which notable SBP and DBP decline were noticed with the combination of Aml/Val SPC (5/80, 5/160, or 10/160 mg) and Aml/Val free dose (5/80, 10/160 mg).

Research[26] in the Eastern Province of Saudi Arabia revealed that females had better DBP control than males. Meanwhile, AlSharqi et al[27] conducted research on Omani hypertensive patients. They reported insignificant changes in both genders' decline SBP and DBP[27]. Trifirò and Spina[28] reported that females respond to antihypertensive therapy compared to males. Two significant randomized, double-blind, placebo-controlled trials comparing amlodipine and valsartan monotherapy to Aml/Val combination therapy and an analysis of its subgroup[29,30]. Such research[29,30] included 3,161 patients with mild to moderate HTN. The baseline alteration for DBP at the end of the eight-week research period served as the primary efficacy objective. Secondary objectives included the proportion of patients with DBP 90 mmHg or >10 with baseline decrease and SBP change. In comparison to either monotherapy at the exact dosage, the efficacy of the combination was higher. More than 80% of patients who received Aml/Val at doses of 5/80 mg, 5/160 mg, or 5/320 mg complied with the response standards. Most patients in the current study utilized Aml/Val SPC strength 10/160 mg (59.1%) rather than Aml/Val SPC 5/160 mg (40.9%). Patients who reached the response crite-

ria for both SBP and DBP were 16.9% and 19.1%, respectively. Patients who met the response criteria for SBP were 30.8% and 44.7%, while those for DBP were 49.2% and 35.1%.

Destro et al[31] also compared Aml/Val to amlodipine monotherapy for systolic stages II and III HTN patients in randomized 8-week trials. Six hundred forty-six patients received treatment, 322 with Aml/Val 5/160 mg and 324 with amlodipine 5 mg over four weeks. At week 4, Aml/Val considerably outperformed amlodipine monotherapy in improved SBP from baseline. After the research, SBP had lowered from a baseline of 171 to 137 mmHg compared to an amlodipine dose of 145 mmHg. Additionally, they discovered that the difference in reaction was the same across all study groups, including those with diabetes, severe hypertension, and elderly participants[31].

In the current study, Aml/Val reduced blood pressure. However, the effect was more pronounced in patients who received 5/160 mg as opposed to 10/160 mg. Patients taking Aml/Val 5/160 mg were able to reduce their SBP by 40%, DBP by 72.3%, and both SBP and DBP by 39.9%, whereas those taking Aml/Val 10/160 mg were able to reduce their SBP by 34.0%, DBP by 73.4%, and both SBP and DBP by 26.6%. These results were consistent with previously reported studies[11]. In addition, with Aml/Val 5/160mg and Aml/Val 10/160 mg, respectively, a dose-dependent reduction in SBP and DBP of -13.6 to -20.98 mmHg and -10.72 to -7.10 mmHg was recorded. These results showed dose-dependent BP decreases for Aml/Val (5/160 mg and 10/160 mg) over a 26-week period, which was partially compatible with previously reported randomized studies[19,29].

Patients under the age of 65 and those with DM, CKD, and CVD with good and effective BP targets and responses were among the patient subgroups included in this study. Previous research[32,33] on Aml/Val SPC administration showed improvements in adherence and durability and decreased healthcare costs when CCB and ARB combos were administered compared to those that were not. Sarkar et al[33] evaluated comorbidity numbers upon blood pressure control and discovered that blood pressure control is the same irrespective of the comorbidities numbers[34]. Saadat et al[35] reported that increasing comorbidities number did not alter compliance. Pechère-Bertschi and Burnier[36] claimed that patients with increasing comorbidities become more concerned about their health and, therefore, more adherence and consistency in treatment.

In this research, the safety of Aml/Val SPC was consistent with randomized and reported previously real-life research[24,31] on Aml/Val SPC. Safety was assessed by incidence of vertigo, respiratory tract infections, ankle edema, and reporting any adverse events (AEs). In the present research, AEs incidence after Aml/Val SPC intake was mostly vertigo (6.3%), respiratory tract infection (4.4%) and ankle edema (2.5%). These results were similar to others[11,19]. Vertigo (6.3%) was an interestingly prominent adverse effect in the current investigation. According to Sung et al[37], most of the drug-related side effects in the Aml/Val combo group were dizziness caused by a more significant fall in blood pressure. Peripheral edema exhibited a decreased frequency of combination treatment (5.4%) compared to amlodipine monotherapy (8.7%) and an increased incidence compared to Valsartan (2.1%) in a trial of 3,155 hypertensive individuals[38]. Messerli[39] and Makani et al[40] reported that both arteriolar and venous resistance with combined therapy was associated with a lower level of peripheral edema. Peripheral edema was reported with low fixed-dose combination therapy, including using CCB as amlodipine. This can be due to a brief observation period, a specific dosage, or minimization of ARB-induced CCB edema, like Valsartan[41]. Randomized 8-week research of 349 Asian patients (mainly Chinese) treated with Aml/Val 5/80 mg did not report incidents of peripheral edema[42]; overall, eight patients had reported peripheral edema [four patients (1.3%) in Aml/Val 5/80mg group, three (1.0%) in Val 80mg group, and one (0.3%) in Val 160 mg group]. Another research[43] recorded a 1.3 % incidence of peripheral edema in 308 Asian patients.

Patients with DM and CKD were included in the current study, and the proportions of patients who met their goal blood pressure were 26.2% and 39.3%, respectively. In DM patients compared to non-DM patients, the change in DBP was much lower, whereas in CKD patients compared to non-CKD patients, there was a significant change in both SBP and DBP. A study[44] comparing the effects of losartan or a placebo on the progression of CKD in 1,513 individuals with T2DM, HTN, and macroalbuminuria found that baseline SBP between 140 and 159 mmHg was associated with a 38% higher risk of end-stage renal disease (ESRD) or death than SBP between 130 and 140 mmHg. Per a ten mmHg increase in baseline SBP, the risk of ESRD or death rises by 6.7% in a multivariate model, but the same increase in baseline DBP lowers the risk by 10.9%. According to the authors, SBP was

a better indicator of renal outcome than DBP, and people with higher base blood pressure were more likely to develop progressive nephropath[44]. In patients with nondiabetic CKD, a goal BP of <130/80 mmHg seems justifiable for those with protein excretion 40.25-0.3 g/day (or albumin excretion 40.15 g/day); a lower BP target of 125/75 mmHg may be applicable for patients with proteinuria 41 g/day. Meanwhile, individuals with normoalbuminuric must be treated to the conventional goal of <140/90 mmHg, as further BP lowering does not confer renal benefits[45]. RAAS inhibitors are particularly successful at slowing progressions towards ESRD, and multifactorial therapeutic approaches like antihypertensive, hypoglycemic, and cholesterol-reduction are frequently advised in guidelines for the early-stage management of renal disease[46]. In 2010, the Yilmaz study[47] in Turkey treated diabetic individuals with Stage-1 CKD with either amlodipine (10 mg/day), valsartan (160 mg/day) or a combination of the two. Combination therapy dramatically improved proteinuria compared to one treatment alone[47]. In this study a significant decrease in UA/CR *vs.* pre-Aml/Val SPC administration in CKD patients. In additional investigations by Kaneshiro et al[48], the effects of amlodipine on individuals using valsartan resulted in a noticeably lower UA/CR, lower blood pressure, and lower pulse wave velocity. The randomized trial by Kashif[49] included 140 CKD patients with baseline blood pressure > 140/90 mmHg and elevated UA/CR. They found that, compared to valsartan alone therapy, valsartan with amlodipine combination therapy significantly lower albuminuria in CKD and improves disease progression[49]. In the study by Fujiwara et al[50], the decline in UA/CR was substantially correlated without regard to nocturnal brachial variations in SBP. They stated that the central BP significantly decreased when valsartan and amlodipine were combined over 24 hours, and they found a unique correlation between the UA/CR and central nocturnal SBP. They concluded that central nocturnal SBP might serve as a therapeutic target for renal safety[50]. Based on the abovementioned, a valsartan and amlodipine combination may be utilized to spot-test the urine albumin/creatinine ratio and administer early prophylaxis to CKD patients with hypertension. This will aid in preventing morbidity and mortality associated with CKD and the progression of renal replacement therapy to ESRD.

Interestingly, in the current study, Aml/Val SPC utilization exhibited a significant increase in vitamin D serum levels in all patients except patients with CKD. Antihypertensive agents' effects on bone metabolism had interesting findings. Djurfeldt et al[51] stated that medications used for CVD treatment, especially antihypertensive drugs, affected bone health. In newly diagnosed hypertension patients, Ay et al[52] investigated the impact of valsartan and amlodipine on vitamin D levels. According to their findings, compared to valsartan, amlodipine dramatically increased vitamin D levels in HTN patients on a 12-week therapy schedule. In addition, a case-control study found that CCBs therapy decreased the likelihood of bone fracture[53]. These results indicated that amlodipine might positively prevent osteoporosis.

Limitations

The limitations of this study are related to the interpretation of its results as it is a non-randomized, open-label, observational, non-controlled study by design, and caution must be employed while deriving conclusions. Another limitation of this study is the use of subjective evaluation scales by physicians to gauge efficacy, acceptability, and adherence to the prescribed course of action. However, due to its strength as an observational study, data could be gathered from a variety of patient demographics with hypertension, increasing the relevance of this study's findings to clinical practice in a real-world scenario.

Conclusions

Many people need at least two antihypertensive drugs to reach their target blood pressure. The single-pill Aml/Val combination offers a monotherapy alternative that is more successful than either component alone. It enables equivalent BP-lowering effects at lower component doses, leading to a decreased incidence of dose-driving drug-associated adverse events. In addition, the SPC reduces the number of tablets a patient may take, simplifies prescription regimes, and could lower out-of-pocket costs by lowering the frequency of doctor visits, all related to higher medication compliance and adherence. The safety and efficacy of Aml/Val SPC in a cohort of Saudi patients are confirmed by this investigation. As a result, both SBP and DBP experienced considerable and early reductions, which enabled many patients to reach their target blood pressure in just 23 weeks. More trials with larger patient populations and longer durations are necessary to evaluate the potential health benefits of this SPC for improving cardiovascular outcomes and organ safety.

Authors' Contributions
All authors contributed significantly to work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation. In addition, all authors took part in drafting, revising, or critically reviewing the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

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Ethics Approval
The study protocol was approved by the Researchers Ethic Committee of King Fahad Armed Forced Hospital in Jeddah, Saudi Arabia (REC# 262).

Availability of Data and Material
Data are contained within the article.

Informed Consent
Patients' consent was taken at hospital admission to use their data with complete confidentiality.

Conflict of Interests
The authors declare no conflict of interest.

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