Efficacy and safety of valsartan and amlodipine single-pill combination in hypertensive patients (PEAK study)

Hipertansiyonlu hastalarda valsartan ve amlodipin tek tablet kombinasyonunun etkinlik ve güvenliliği (PEAK çalışması)

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ABSTRACT

Objectives: This study was designed to assess the safety, compliance and efficacy of amlodipine (Aml) and valsartan (Val) single-pill combination (SPC) in a large hypertensive patient population.

Study design: This is a non-interventional, observational, open label study conducted in 166 centers in Turkey with a 24-week follow-up period.

Results: Of the 1184 enrolled patients, two-thirds were female (62.2%). The mean age was 57.7±11.3 years, and 26.1% of the patients were older than 65 years. The majority of patients (82.3%) were overweight or obese. During the course of the study, 150 (12.7%) patients experienced a total of 174 adverse events (AEs). The overall mean (SD) compliance rate was determined to be 96.9 (0.2)%. The most commonly reported AE was edema, with a new-onset edema incidence of 6.7%. In the entire group, Aml/Val SPC significantly reduced both systolic and diastolic blood pressure (BP), with a reduction of 29.6±0.9 / 14.7±0.6 mmHg (for each, p<0.001).

Conclusion: As a result of the low incidences of AEs and new-onset edema, the safety profile of Aml/Val SPC proved to be optimal. Aml/Val SPC reduced BP efficiently and met the needs of most patients to achieve the targets. Aml/Val SPC seems to be a beneficial option for effective BP control, which is a key factor influencing cardiovascular outcome.

ÖZET

Amaç: Bu çalışmada, amlodipin (Aml) ve valsartan (Val) tek tablet kombinasyonunun (TTK), hipertansiyonlu Türk hastalardaki güvenlilik, uyum ve etkinliğinin değerlendirilmesi hedeflendi.

Çalışma planı: Girişimsel olmayan, gözlemsel ve açık etiketli çalışma 166 merkezde gerçekleştirildi, hastalar 24 hafta süre ile izlendi.

Bulgular: Çalışmaya üçte ikisi (%62) kadın olmak üzere 1184 hasta alındı. Ortalama yaş 57.7±11.3 olup, hastaların %26.1'i 65 yaşın üzerinde idi. Hastaların çoğunluğu (%82.3) fazla kilolu ya da obezdi. Çalışma boyunca 150 hastada (%12.7) toplam 174 istenmeyen olay bildirildi, bunların %96.9'u (0.2) ciddi olmayan yan etki olarak tanımlandı. En sık görülen yan etki ödem olup, yeni başlayan ödem insidansı %6.7 idi. Tüm grupta Aml/Val TTK sistolik ve diyastolik kan basınçlarını başlangıca göre anlamlı olarak düşürdü (sırasıyla 29.6±0.9 ve 14.7±0.6 mmHg herbiri için, p<0.001).

Sonuç: Amlodipin/valsartan TTK ile elde edilen etkin kan basıncı düşüşleri ile, hastaların büyük kısmı hedeflenen kan basıncı değerlerine ulaşmıştır. Düşük istenmeyen olay ve yeni başlayan ödem oranlarıyla Aml/Val TTK'nın güvenli bir tedavi ve kardiyovasküler olayların sonuçlarına çok önemli etkisi olan kan basıncı kontrolünün sağlanmasında faydalı bir seçenek olduğu gösterilmiştir.

In light of the continuously increasing occurrence of hypertension (HTN) and its established relations to morbidity and mortality, HTN has been reported as one of the major causes of death and disease in both developing and developed countries.[1-4] The meta-analysis by Lewington et al.[2] clearly revealed that a 20/10 mmHg increase in systolic and diastolic blood pressure (SBP, DBP) on a healthy BP of 115/75

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mmHg may double the risk of cardiovascular diseases. Based on these and other similar findings, the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) have endorsed the employment of aggressive anti-HTN treatment procedures in their 2007 guidelines, which include cardiovascular risk evaluations for each patient in order to establish treatment targets, the usage of two-drug combinations for initial treatment to reach BP targets, and the addition of lipid-lowering and anti-platelet treatments to anti-HTN treatments in order to reduce overall cardiovascular risks.[5,6]

One of the major challenges that still exist regarding HTN treatment is that many patients cannot achieve BP targets despite there being an extensive range of anti-HTN drugs available in the market.[7] Recent data have revealed that of the 73% of the HTN patients treated in the United States of America (USA), only 69% of them achieved BP targets of 140/90 mmHg, whilst the overall control rate was 50%.[8] The results of another recent survey in Central and Eastern Europe showed that BP control could be achieved in only 27% of treated HTN patients, despite common usage of combination-drug treatments.[9] Similar findings also emerged for the rest of Europe: Kjeldsen et al. reported that BP was controlled in only 28% of all HTN patients in five selected Western European countries, whilst Wang et al. revealed that the BP control rate amongst treated patients in Western Europe varied between 31% and 46%.[10,11]

The data collected in Turkey are similar to those of other European countries. A 2003 analysis of a HTN prevalence study revealed that BP control rates were 8% for all HTN patients and 21% for treated patients.[12] The results of a subsequent incidence study in 2007 showed that the overall BP control rates for HTN patients rose to 14%, whilst the ones in treated patients increased to 27%.[13]

Although control rates in the USA and throughout Europe (including Turkey) have significantly risen over the past two decades compared to previously published survey results, it has become clear that there is still room for improvement in the management of HTN.[1]

The ESC/ESH guidelines recommend combinations of calcium channel blockers (CCB) and angiotensin II receptor blockers (ARBs) for HTN treatment based on their proven efficacy and safety. Single-pill combinations (SPCs) are found to be advantageous as they are far easier to administer compared to free combinations, and they also improve patient compliance to the treatment.[5] Amlodipine (Aml) and valsartan (Val) SPC is the first of its kind that is available in the market, which contains a complementary mechanism of action of dihydropyridine CCB and a selective angiotensin type 1 receptor antagonism.[14]

Abbreviations:

AEs	*Adverse events*
Aml	*Amlodipine*
ARBs	*Angiotensin II receptor blockers*
BP	*Blood pressure*
BMI	*Body mass index*
CCB	*Calcium channel blockers*
CR	*Compliance rate*
DBP	*Diastolic blood pressure*
ESC	*European Society of Cardiology*
ESH	*European Society of Hypertension*
HCR	*High compliance rate*
HTN	*Hypertension*
ISH	*Isolated systolic hypertension*
ITT	*Intent-to-treat*
IQR	*Interquartile range*
PP	*Per-protocol*
RCTs	*Randomized controlled trials*
SAEs	*Serious adverse events*
SBP	*Systolic blood pressure*
SD	*Standard deviation*
SPCs	*Single-pill combinations*
Val	*Valsartan*

The efficacy and safety of Aml/Val SPC have been proven in many previous randomized controlled trials (RCTs).[14] The primary objective of this study was to assess the safety profile of Aml/Val SPC in a large HTN patient population in real-life setting. The patient compliance and efficacy of Aml/Val SPC were also assessed as a secondary objective.

PATIENTS AND METHODS

This is a non-interventional, observational single-arm study designed to determine the safety and efficacy of Aml/Val SPC treatment in a real-life outpatient setting. Hypertensive patients admitted to 166 primary, secondary or tertiary outpatient clinics throughout Turkey from March 2009 to October 2010 were enrolled in the study. The follow-up period ended in March 2011.

Prior to enrollment, the objectives, procedures, and risks and benefits of taking part in the study were explained to the patients, and all participating patients provided their signed informed consent before entering the study. The study was designed, conducted and reported in full accordance with local observational study guidelines, and International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and relevant European Union Directives.[15-17] The ethics committee of the coordinator investigator's hospital and the Turkish Ministry of Health reviewed

and approved the study protocol, Consent Form and Case Report Form before any study-related activity could start. The authors used the STROBE statement and its explanatory papers as guides to publish the results of the study.[18]

Study population

Adult HTN patients (18+ years of age) of both genders who had already been on either 5/160 mg or 10/160 mg Aml/Val SPC at baseline were included in the study. To be eligible, Aml/Val SPC should have been started in the last two weeks prior to the study enrollment. Patients suffering from serious illnesses that could have affected the study procedure and evaluation (according to the investigator's discretion), patients who had experienced an allergic reaction or hypersensitivity to Aml/Val SPC, and pregnant or lactating women were excluded from the study.

The investigators selected the participants from their personal outpatient patient database. The patient assignment method had not been decided in advance and the administration of Aml/Val SPC was clearly separate from the decision of inclusion.

Study drug

Aml/Val SPC was recommended as 5/160 mg or 10/160 mg once a day as described in the approved summary of the product's characteristics. All investigators were advised to prescribe the study drug and to titrate the dose to achieve BP targets during the study in full accordance with the terms of the marketing authorization.

Aml/Val SPC was either used as the first anti-HTN treatment or patients may have been switched from a previous medication by a physician. If any patient had been administered additional anti-HTN drugs (except thiazide diuretics) during the study, the patient was excluded from the study to ensure uncontaminated observations on the safety and efficacy of Aml/Val SPC.

Study procedures

The study protocol recommended each patient to be followed up on a 24-week basis. The investigators were advised to invite the patients to at least three follow-up visits preferably four, 12 and 24 weeks after the baseline visit, but the interval and frequency of follow-up visits were left to the investigator's discretion, due to the non-interventional design of the study.

Data relating to patient demographics, HTN history, and previous anti-HTN treatments (if used) were recorded at the baseline visit. In addition, at baseline and at each follow-up visit, the investigators measured BP and other vital signs, performed a full body examination, recorded the presence of edema, inquired about other adverse events (AEs) and existing or concomitant treatments and diseases, and recorded treatment details. The existence, severity, and casual relationship of AE with Aml/Val SPC were determined according to the investigator's discretion. No additional diagnostic or monitoring procedures other than those already performed by the investigators on a daily basis were offered to the patients because of their participation in the study.

BP measurements were taken by the investigator at least twice from both right and left arms with patients at rest (after 5-10 min in the sitting position) with a validated mercury sphygmomanometer and appropriate cuff size for each patient (larger sizes for obese patients) in full accordance with the guidelines. At each visit, the highest measurement was used as the final measurement.[19]

Study variables

The primary safety outcome was the incidence of AEs and serious adverse events (SAEs). Type, severity, onset, duration, and the results of AEs and the causality relationship with Aml/Val SPC were set as secondary safety outcomes. In particular, the existence and severity (mild, moderate or severe) of edema was evaluated in detail, since it commonly occurs during Aml treatment.

The severity of edema was clinically justified as mild (barely perceptible pit formation on pressing a thumb or finger on the surface of the limb or body surface being examined), moderate (significantly visible pit formation on pressing a thumb or finger on the surface of the limb or body surface being examined, but with the pit thus caused disappearing quickly on removal of pressure), and severe (deep well-outlined pit formation on pressing a thumb or finger on the surface of the limb or body surface being examined, with the pit thus caused lasting several seconds on removal of pressure).

Patient compliance to treatment was evaluated based on records kept during the study of the study medication used, dosages administered, and intervals

between visits. Patients were asked to return all unused medication and empty blisters at each visit and at the end of the study. Pill counting was performed by investigators at each visit and reported in the relevant part of the Case Report Form.

The compliance rate (CR) was calculated by taking the amount of drug ingested divided by the amount the patient should have ingested and multiplying by 100. The patients were classified in CR >80% group (high [HCR]) and CR ≤80% group (low [LCR]).

The absolute changes in SBP and DBP from baseline were the primary efficacy outcomes. The other efficacy outcomes were the ratio of patients who achieved BP targets (≤140/90 mmHg) and the response rates that had been defined as to achieve a DBP <90 mmHg or ≥10 mmHg reduction in DBP compared to baseline.[20]

Statistics

A prior sample size calculation was performed based on the concept of a study with no background incidence of a particular adverse reaction since no previous AE incidences with Aml/Val SPC in Turkey had been published.[21] The probability of observing at least one particular AE among 1919 patients is generally 0.10, which in turn, achieves a 90% power, when an anticipated incidence is 0.0012 in the general population.

At the end of the 18 months' enrollment period, a post-hoc power analysis revealed that a sample size of 1184 achieves at least 80% power; therefore, patient enrollment was stopped before reaching the original patient number.

The data collected from of all participating patients (n=1184) were included in the safety population for safety analyses. The per-protocol (PP) population included the data of patients who had fulfilled the protocol in terms of follow-up. The intent-to-treat (ITT) population included the data of all patients who attended at least one follow-up visit. Safety analyses were performed studying the safety population, while efficacy analyses were performed in the PP population. Efficacy analyses were also performed in the ITT population, and the results were compared to those from the PP population. All analyses were also repeated in predefined subgroups (diabetic patients, ESH/ESC BP classification, body mass index [BMI], and age groups).[5]

Counts and percentages were used to summarize categorical variables. The continuous variables were summarized as mean (with standard deviation [SD] or standard error [SE]) or median (interquartile range [IQR]), and analysis of covariance for repeated measures was used to assess the continuous variables during the course of the study. Time to each visit from baseline and study center were used as pre-defined covariants in analyses. Categorical variables were compared by using chi-square test, and linear correlation was evaluated with Pearson linear correlation test. No specific methods were used to address missing data, but the number of missing data for each variable of interest and for each step in the analysis was reported.

RESULTS

In total, 1184 patients who had started using Aml/Val SPC in the last two weeks before enrollment were included, and of these, 662 (55.8%) patients completed the study. The main reason for discontinuation was lost to follow-up (416 patients, 35.1%) (Fig. 1).

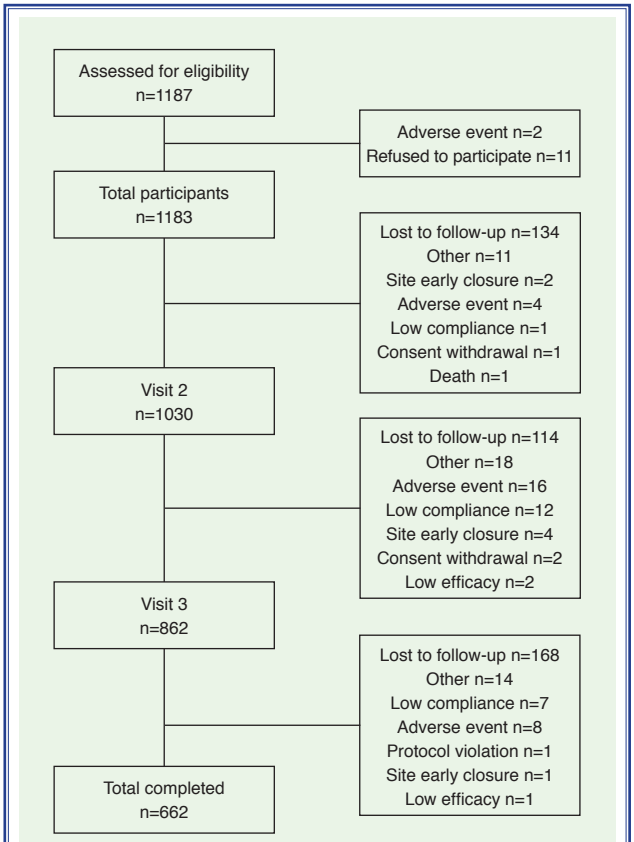

Figure 1. Study flow diagram.

The first, second and third follow-up visits were conducted at a median (IQR) of 30 (5) (range: 4-288), 90 (11) (range 28-400) and 178 (17) (range: 77-422) days after the baseline visit, respectively.

Two-thirds of the patients were female (62.2%), and all patients were Caucasians. The mean (SD) age was 57.7±11.3 years, and 26.1% of the patients were older than 65 years. The majority of the patients (n=974, 82.3%) were overweight or obese and the mean (SD) BMI was 30.0±5.6 kg/m^2 (Table 1).

Almost half of the patients (n=543, 45.9%) had previously used other anti-HTN drugs, and then switched to Aml/Val SPC. The most commonly used drugs were angiotensin converting enzyme inhibitors (ACEi) and ARBs as monotherapy or in combination with other anti-HTN drugs. The main reason for the switch was the lack of efficacy (Table 2).

Table 1. Patient demographic and basic characteristics

	Value	
	n (%)	Mean±SD (range)
Age (years)		57.7±11.3 (50-65)
<65	875 (73.9)	
≥65	309 (26.1)	
Gender		
Female	737 (62.2)	
Male	447 (37.8)	
BMI (kg/m^2)		30.0±5.6 (12.5-59.2)
<25.0	198 (16.7)	
25.0 to <30.0	436 (36.8)	
≥30.0	538 (45.4)	
Unable to calculate	12 (1.0)	
Diabetic patients	98 (8.3)	

BMI: Body mass index; SD: Standard deviation.

Table 2. Previous anti-hypertensive history

	n	%
Previous anti-hypertensive treatment	543	45.9
Angiotensin II receptor blockers*	138	11.7
Angiotensin converting enzyme inhibitors*	134	11.3
Calcium channel blocker*	69	5.8
Beta blocker*	65	5.5
Diuretic monotherapy	29	2.4
Others	6	0.5
Not reported	102	8.6
Reason for switching to Aml/Val SPC†		
Lack of efficacy	489	41.3
Adverse events	32	2.7
Poor patient compliance	53	4.5
Other	3	0.3

* As monotherapy or in combination with other anti-hypertensive drugs.
† More than one reason could have been reported.

Dosage and duration of Aml/Val SPC treatment

Aml/Val SPC treatment was the first-line antihypertensive medication in 54.0% (n=641) of patients, while switching from other antihypertensive medications to Aml/Val SPC treatment was identified in 46.0% (n=543) of patients mainly due to inefficacy (90.0%), AEs (6.0%) and poor patient compliance to treatment (10.0%).

The dosage of Aml/Val SPC treatment was 5/160 mg in 45.7% (n=541), while it was 10/160 mg in 54.3% (n=643) of the overall study population. When timing of HTN diagnosis was considered, the dosage of ongoing Aml/Val SPC treatment was 5/160 mg in 41.1% (n=223) and 10/160 mg in 58.9% (n=320) of patients with a history of HTN (n=543), while it was 5/160 mg in 49.6% (n=318) and 10/160 mg in 50.4% (n=323) of patients with newly diagnosed HTN (n=641).

No change in dosage was the most common therapeutic decision in both 5/160 mg (91.3%) and 10/160 mg (98.6%) doses of Aml/Val SPC treatment during the follow-up period. Duration of Aml/Val SPC treatment was a mean (SD) 139.6±67.9 days, with a median of 166 days, ranging from 5 to 422 days.

Treatment compliance

The overall mean (SD) CR was determined to be 96.9±0.2%, while HCR was identified in 94.0% of the study population. At visits 2, 3 and 4, the mean (SD) CR percents were 97.1±0.2, 97.9±0.3 and 97.0±0.2%, with achievement of HCR in 94.0, 93.0 and 92.0% of patients, respectively. A slight reduction in mean(SD) CR was determined in case of longer intervals between consecutive follow-up visits (rho = -0.36, p<0.0001).

Adverse events

The analysis revealed that AE incidence during 24 weeks of Aml/Val SPC treatment was low, as during

the course of the study, 150 (12.7% of safety population) patients experienced a total of 174 AEs, and a total of 5 SAEs were reported in 5 patients. Most of the AEs (71.8% of AEs) were reported to be mild, and no action was taken for 101 AEs (58.0% of AEs) (Table 3).

The most commonly reported AEs were edema, headache, dizziness, and pain, with incidences of 10.8%, 0.4%, 0.3%, and 0.3%, respectively (Table 4). No AEs regarding any laboratory parameters, including study medication-related parameters (e.g. potassium, sodium, creatinine, blood urea nitrogen, glomerular filtration rate), were reported. Multiple injuries (1 patient), congestive heart failure (1 patient), angina pectoris (1 patient), hypotension (1 patient), and gastroenteritis (1 patient) were the reported SAEs. Out of these 5 SAEs, only hypotension was suspected to be related to Aml/Val SPC treatment. Gastroenteritis and multiple injuries resulted in death, and the other SAEs recovered completely. Three-quarters of AEs (77.0% of AEs) were suspected to be related to Aml/Val SPC treatment by the investigators (Table 5).

Table 3. Characteristics of adverse events (AEs)

	n	%*
Patient experienced AEs	150	12.7
Experienced only 1 AE	132	11.1
Experienced 2 AEs	12	1
Experienced 3 AEs	6	0.5
Total AE number	174	
Total SAE number	5	
	n	%†
Severity of AE		
Mild	125	71.8
Moderate	34	19.5
Severe	11	6.3
Not reported	4	2.3
Action taken		
No action taken	101	58.0
Aml/Val SPC dose reduced or delayed	19	10.9
Aml/Val SPC discontinued	26	14.9
Other	24	13.8
Not reported	4	2.3

* Patient count, percent of safety population (n=1184).
† Percent of AEs (n=174).
AEs: Adverse events; SAE: Severe adverse event.

Table 4. Reported adverse events

Adverse events	n	%*
Edema	128	10.8
Headache	5	0.4
Dizziness	3	0.3
Pain	3	0.3
Flushing	2	0.2
Hypotension	2	0.2
Other†	14	1.2

* Patient count, percent of safety population (n=1184).
† Each adverse event was observed in only one patient.

Table 5. Causal relationship of adverse events with Aml/Val SPC

	n	%*
Not suspected	36	20.7
Suspected	134	77.0
Edema	118	67.8
Headache	3	1.7
Dizziness	2	1.1
Flushing	2	1.1
Hypotension	2	1.1
Pain	2	1.1
Diarrhea	1	0.6
Hypervolemia	1	0.6
Not reported	4	2.3

* Percent of AEs (n=174).
Aml/Val: Amlodipine/Valsartan; SPC: Single-pill combination.

Since edema is highly common with Aml treatment, additional data on the occurrence of edema were collected. At baseline, 81 (6.8%) patients had already shown traces of edema, and edema resolved in 48 (4.1%) of these patients after administration of Aml/Val SPC. New-onset edema was observed in 79 (6.7%) patients during the course of the study. The severity of edema was mostly reported as mild (74.1%) and moderate (22.9%), and only 3.1% of edema occurrences were reported to be severe.

Blood pressure measurements, control rates and response rates

In the PP population, baseline BP was 164.2±0.9/95.8±0.6 mmHg. At the final visit, with a

median of 178 days after baseline, a significant mean reduction of 29.6±0.9 mmHg in SBP and of 14.7±0.6 mmHg in DBP were observed (for each, p<0.001). BP declined to 134.6±0.5)/81.2±0.3 mmHg (Fig. 2). In the ITT population, the reduction was 33.4±0.8/17.5±0.5 mmHg (from 164.7±0.8/98.0±0.5) mmHg at baseline to 131.3±0.5/80.5±0.3 mmHg at the final visit) (for each, p<0.001).

Among the diabetic PP population, BP lowered to 130.3±1.7/80.9±0.7 mmHg at the final visit from 166.4±2.8/97.2±1.4 mmHg at the baseline, with a significant reduction of 36.1±2.7/16.3±1.5 mmHg (for each, p<0.001). In the diabetic ITT population, the reduction was 35.8±2.7/16.0±1.4 mmHg (from 166.6±2.2/96.0±1.3 mmHg at baseline to 131.0±1.5/81.2±1.1 mmHg at the final visit) (for each, p<0.001).

The observed reductions were highly correlated with the baseline BP; higher BP reductions were observed as the baseline BP level rose. In patients with baseline SBP ≥180 mmHg, BP decreased 52.5±1.3/21.0±1.0 mmHg, whereas the decrease was 12.4±1.1/9.6±0.9 mmHg in those with baseline SBP <160 mmHg (Table 6). Among patients with isolated systolic hypertension (ISH), SBP significantly reduced (p<0.001), whereas no significant changes in DBP were observed (Table 6). Blood pressure reductions in age and BMI subgroups were statistically significant and did not vary among subgroups (Table 6).

Blood pressure control rate dramatically increased to 86.9% at the last visit from 8.9% at baseline (p<0.001). Similarly, a vast majority of the patients in baseline BP subgroups, diabetic patients and patients

Table 6. Blood pressure reduction in pre-defined subgroups

Subgroup		SBP/DBP (mmHg)*			p†
	n‡	Baseline	Final visit	Reduction	
Baseline SBP (mmHg)					
<160	PP	142.4±0.8 / 88.2±0.7	130.0±0.8 / 78.6±0.5	12.4±1.1 / 9.6±0.9	<0.001
	ITT	143.0±0.6 / 90.0±0.6	129.2±0.8 / 78.9±0.5	13.7±1.0 / 11.5±0.8	<0.001
160 to <180	PP	166.2±0.4 / 97.3±0.6	132.9±0.6 / 80.5±0.4	33.3±0.7 / 16.8±0.7	<0.001
	ITT	165.7±0.3 / 98.5±0.5	131.0±0.7 / 80.5±0.4	35.0±0.8 / 18.6±0.7	<0.001
≥180	PP	187.9±1.0 / 103.8±0.9	135.4±0.9 / 82.8±0.6	52.5±1.3 / 21.0±1.0	<0.001
	ITT	190.0±0.7 / 105.3±0.6	134.2±1.0 / 82.3±0.5	54.1±1.2 / 23.0±0.9	<0.001
Isolated systolic hypertension					
	PP	157.7±1.1 / 81.1±0.6	138.9±1.2 / 78.6±0.7	18.8±1.6 / 2.5±0.9	<0.001, 0.064
	ITT	158.4±1.3 / 80.4±0.5	137.7±1.9 / 78.5±0.8	19.9±2.2 / 2.2±0.9	<0.001, 0.107
Age (years)					
<65	PP	167.1±1.5 / 95.3±1.1	131.5±0.8 / 80.0±0.5	35.6±1.5 / 15.4±1.2	<0.001
	ITT	165.7±0.7 / 98.1±0.4	131.4±0.5 / 80.6±0.3	32.5±1.0 / 17.6±0.6	<0.001
≥65	PP	167.1±1.5 / 95.3±1.1	131.5±0.8 / 80.0±0.5	35.6±1.5 / 15.4±1.2	<0.001
	ITT	168.6±1.2 / 97.9±0.8	130.9±0.9 / 80.1±0.5	36.2±1.7 / 17.4±1.1	<0.001
Body mass index (kg/m^2)					
<25	PP	165.5±1.6 / 94.6±1.1	134.7±1.3 / 80.2±0.7	30.9±1.8 / 14.4±1.3	<0.001
	ITT	166.6±1.4 / 96.0±0.9	132.1±1.4 / 79.7±0.7	32.8±1.8 / 15.7±1.1	<0.001
25 to <30	PP	164.8±1.3 / 96.6±0.8	132.7±0.7 / 79.5±0.5	32.1±1.3 / 17.1±0.8	<0.001
	ITT	166.2±1.0 / 98.4±0.6	130.5±0.8 / 79.6±0.5	34.0±1.4 / 18.6±0.8	<0.001
≥30	PP	163.0±1.2 / 97.8±0.7	131.8±0.6 / 81.9±0.4	31.3±1.2 / 15.9±0.8	<0.001
	ITT	166.7±0.9 / 98.6±0.5	131.6±0.6 / 81.4±0.4	33.2±1.3 / 17.4±0.8	<0.001

* SBP/DBP: Systolic / diastolic blood pressure, results are given as mean (standard error). † P value for both SBP and DBP for final visit versus baseline comparison, unless given separately. ‡ n for PP population=662, for ITT population=1030.

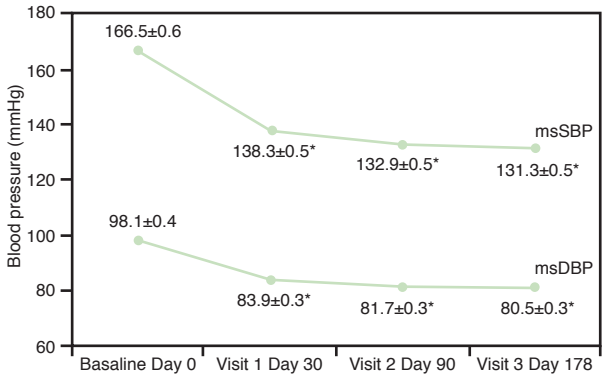

Figure 2. Systolic (SBP) and diastolic blood pressure (DBP) levels during the course of the study, mean(SE), *p<0.001 vs. baseline, in PP population (n=662).

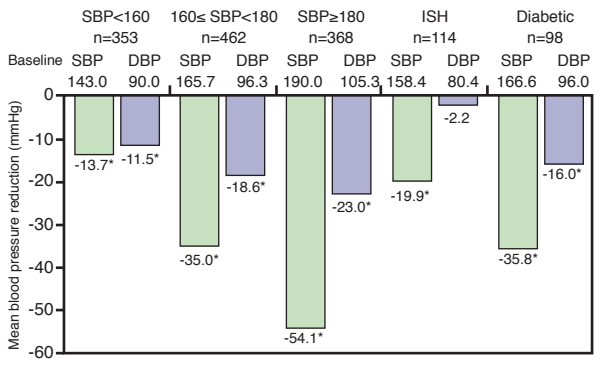

Figure 3. Blood pressure control rates in baseline systolic blood pressure (SBP) subgroups, patients with isolated systolic hypertension (ISH) and diabetes mellitus. At the end of follow-up (median 178 days).

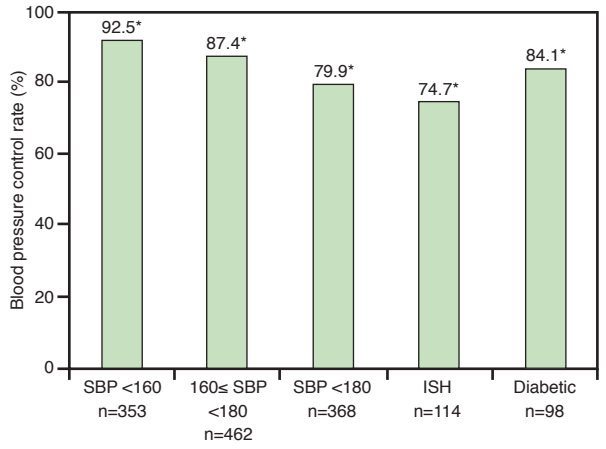

Figure 4. Response rates in baseline systolic blood pressure subgroups, patients with isolated systolic hypertension (ISH) and diabetes mellitus, at the end of follow-up (median 178 days).

with ISH, achieved BP targets at the last visit (Fig. 3).

Upon responder rate evaluation, in the entire group, 95.0% of patients were responders, and baseline BP levels did not affect responder rates. The vast majority of diabetic patients and patients with ISH were also responders, 90.5% and 96%, respectively (Fig. 4).

DISCUSSION

We aimed to assess the safety and efficacy of Aml/Val SPC in HTN patients in a real-life setting. The study results demonstrated that during the course of the study (approximately 24 weeks), the reported AE incidence rate had been relatively low, Aml/Val SPC significantly reduced BP, and the majority of patients had achieved optimal BP targets. Most of the incidents had been evaluated as mild, and no action had to be taken for more than half of them. Aml/Val SPC did not cause any permanent SAEs. A small number of patients experienced new-onset edema, whereas in almost two-thirds of patients with edema at baseline, their edema recovered during the course of the study.

The results from PP and ITT populations of the study are similar to those of previously reported RCTs and observational studies conducted with Aml/Val SPC or free combinations. Philipp et al.[22] and Smith et al.[23] revealed that Aml/Val SPC provided a significant BP lowering effect; the highest reductions were observed in patients with a higher baseline BP, and most of the patients achieved optimal BP targets. Apart from these randomized placebo- controlled studies, similar results were found in an observational study conducted by Chazova et al.[24] investigating free combinations of Aml/Val in a real-life setting. They reported a 33.2/16.9 mmHg reduction in SBP and DBP, and 76% of patients were under the BP targets of 140/90 mmHg at the end of the 12 weeks. They also observed an increasing BP reduction as the baseline BP level rose. Our results corroborate with this previous study in a real-life setting.

Patients with SBP >180 mmHg have always had difficulties in achieving BP targets. Aml/Val SPC was shown to provide a significant reduction of 43.0 mmHg in patients with grade 3 HTN over six weeks. Although this reduction was statistically significant, the sample size of the relevant subgroup was considerably small.[25] Similarly, Chazova et al.[24] reported

a 55.5 mmHg mean SBP reduction for patients with baseline BP >180 mmHg over 12 weeks after Aml/Val free combination administration. These results indicate that Aml/Val SPC is an effective drug for such patients. Our study was one of the first studies having an adequate sample size to show that Aml/Val SPC provides significant BP reduction in patients with baseline SBP ≥180 mmHg.

Another challenging patient group to achieve BP targets and to be protected from target organ damage is diabetic patients. ESC/ESH HTN guidelines classify diabetic HTN patients as a high added-risk group if their BP is higher than 130/80 mmHg. Diabetic HTN patients are advised to use ARBs as a monotherapy or usually in combination with other drugs due to their renoprotective effects.[5,6] Moreover, as an ARB/CCB combination, Aml/Val SPC has been demonstrated in a recently published study to improve insulin sensitivity.[26] In addition to these mechanistic benefits, Allemann et al.[27] reported a substantial rise in BP control rates up to 92% in diabetic patients under various Aml/Val SPC treatments. Similarly, diabetic patients in our study benefitted from Aml/Val SPC and achieved the aimed BP targets.

Isolated systolic hypertension was pointed out as a risk factor for elderly HTN patients in ESC/ESH guidelines, which stated that low diastolic BP could cause additional cardiovascular risks.[5] Therefore, anti-HTN drugs are expected to lower only systolic BP in patients with ISH. In the study by Chazova et al.,[24] patients with ISH were treated using an Aml/Val combination as required, without observing any significant reduction in diastolic BP. Our results have confirmed and revealed that Aml/Val SPC is an efficacious treatment to reduce BP based on the individual requirement of each patient type.

It has been hypothesized that CCBs could cause arterial vasodilatation, which could result in decreased total peripheral resistance. This effect could lead to BP reduction and an increase in capillary hydrostatic pressure, with consequent transcapillary fluid loss. On the other hand, ARBs dilate veins as well as arteries. This venous vasodilatation can normalize the capillary hydrostatic pressure elevated by CCB.[28] Fogari et al.[28] conducted a study to investigate the effect of the concomitant use of Aml and Val on edema formation using well-defined objective measurement methods. Their results showed that the Aml/Val combination may decrease not only the incidence rate but also the severity of edema. In another study, in which the evaluation of the presence of edema was based on investigator examination, the results showed that switching to the Aml/Val SPC treatment can aid in the disappearance of edema in 50% of patients who experienced edema with Aml monotherapy.[29] The study of Chazova et al.[24] obviously supports the results of these two studies in real-life settings.

Aml/Val SPC was well tolerated. The observed AEs (excluding edema) were common symptoms, and their frequencies were very low. Although edema was the most commonly reported AE in our study as an expected result of Aml administration, the incidence of new-onset edema was considerably low, indicating that combined use of Aml and Val might have aided in the disappearance or reduction of existing edema.

A recent survey showed that physicians may hesitate to start or replace the medication in HTN patients.[30] Although guidelines recommend the use of anti-HTN treatments for even stage 1 HTN patients to decrease overall cardiovascular risk, most physicians (>90%) will not take immediate action insofar as HTN treatment is concerned unless the BP levels of their patients are higher than 168/100 mmHg, according to the results of this survey. The results of this interesting survey revealed that even unsatisfactory treatment results may be evaluated as a normal outcome by physicians, and patients may be exposed to high risk even when they are undergoing treatment. Therefore, when a physician decides to start anti-HTN treatment, an efficacious and tolerable treatment such as Aml/Val SPC should be selected to maximize the risk reduction.[30]

One of the major limitations of our study was its design. Due to the nature of non-interventional and observational study designs, the ratio of patients who did not complete the study was considerably high. Although every possible effort was made by investigators, almost one-third of the patients could not be reached by the end of the study. The reason for such a high lost-to-follow-up rate might be an occurrence of AE in those patients. Although overall AE incidence was considerably low in the safety population of the study, the possibility that an experienced AE may have been the main cause of a patient's being lost-to-follow-up cannot be excluded. However, we believe that the main reason for such a high dropout rate is

the health care system in Turkey itself. The current system allows the patients to select their physicians and hospitals and does not stipulate the visiting family physician before admission to second- or third-level health care institutions; moreover, it covers all medical expenditures, even if those were made for the same medical condition by different institutions in a short period. Thus, it is highly common to admit to different physicians for the same medical conditions, especially for chronic conditions. One of the other limitations was that the observational one-arm design may not allow us to draw certain conclusions about Aml/Val SPC, but the efficacy and safety of Aml/Val SPC versus placebo or active comparator have already been established in several previous RCTs. Therefore, our study aimed to evaluate the conditions in a real-life setting, which may be different from a RCT. Additionally, although every procedure was defined and explained in the study protocol, most of the measurements (e.g. BP, height, weight, edema evaluation) were based on the physician's discretion, which might have caused non-standardized measurements. The selection method of patients for the study probably caused a selection bias that precludes generalization of the results to the entire population. The recording of the presence of edema at each visit, taken separately from daily routine investigations, might have caused a detection bias that probably resulted in higher edema incidence.

In conclusion, as a result of the low incidences of AEs and new-onset edema, the safety profile of Aml/Val SPC proved to be optimal. Aml/Val SPC reduced blood pressure efficiently and met the needs of most patients to achieve the targets defined in the guidelines (e.g. severe HTN, diabetic, ISH). Aml/Val SPC seems to be a good option for effective BP control, which is a key factor that influences cardiovascular outcome.

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