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Original article

Real-world clinical experience of amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide in hypertension: the EXCITE study

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Abstract

Objective:
The EXCITE (clinical EXperienCe of amlodIpine and valsarTan in hypErtension) study was designed to evaluate the effectiveness, tolerability and adherence of amlodipine/valsartan (Aml/Val) and amlodipine/valsartan/hydrochlorothiazide (Aml/Val/HCT) single-pill combination therapies in patients with hypertension from the Middle East and Asia studied in routine clinical practice.

Research design and methods:
This was a prospective, multinational, non-interventional real-world study in which adult patients with hypertension receiving treatment with Aml/Val or Aml/Val/HCT as part of routine clinical practice were observed for a period of 26 ± 8 weeks. Dosages in milligrams (prescribed in accordance with local prescribing information) were Aml/Val: 5/80, 5/160, 10/160, 5/320 or 10/320; Aml/Val/HCT: 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25 or 10/320/25.

Main outcome measures:
Treatment effectiveness was assessed by change from baseline in mean sitting systolic blood pressure (BP)/diastolic BP (msSBP/msDBP), and the proportion of patients achieving therapeutic goal and BP response. Safety and tolerability were also assessed.

Results:
Of 9794 patients analyzed (mean age 53.2 years), 8603 received Aml/Val and 1191 Aml/Val/HCT. At study end (26 ± 8 weeks), overall msSBP (95% confidence interval [CI]) reductions from baseline were −31.0 (−31.42, −30.67) mmHg for Aml/Val and −36.6 (−37.61, −35.50) mmHg for Aml/Val/HCT; msDBP reductions from baseline were −16.6 (−16.79, −16.34) mmHg for Aml/Val and −17.8 (−18.41, −17.22) mmHg for Aml/Val/HCT. Meaningful reductions in BP from baseline were also consistently observed across all Aml/Val dosages and severities of hypertension. Adverse events (AEs) were reported in 11.2% and 6.1% of patients in the Aml/Val and Aml/Val/HCT groups, respectively. Most frequently reported AEs in the Aml/Val and Aml/Val/HCT groups were edema and peripheral edema. While the observational design of the study has inherent limitations, it enables collection of real-world data from a more naturalistic clinical setting, and the large size of the study increases the robustness of the study, as indicated by the narrow confidence intervals for the main study outcomes.

Conclusions:
The EXCITE study provides evidence that Aml/Val and Aml/Val/HCT provide clinically meaningful BP reductions and are well tolerated in a large multi-ethnic hypertensive population studied in routine clinical practice.

Introduction

The worldwide prevalence and disease burden of hypertension are both high. According to a comparative risk assessment of deaths and disability-adjusted life years in 21 regions between 1990 and 2010, high blood pressure (BP) ranked as the leading risk factor for disease burden in the Middle East and most of Asia, as well as most of Latin America, North Africa and Central Europe[1]. Almost 75% of patients with hypertension (639 million people) reside in economically developing regions of the world[2], and these regions are projected to have the largest increase in hypertension prevalence by 2025[2,3]. The significant mortality attributed to hypertension and associated diseases[4] reinforces the need to broaden the scenarios under which antihypertensives are assessed. The Middle East and Asia are examples of regions where hypertension prevalence and disease burden are rising[3,5], but study data collected on the use of antihypertensives, including single-pill combinations (SPCs), in these populations are limited.

Achieving and sustaining BP control is the ultimate challenge in hypertension therapy[6–9]. BP control rates are generally low globally and can be as low as 9.8% for men and 16.2% for women in economically developing regions[10]. There are numerous reasons for poor BP control rates, including suboptimal antihypertensive treatment efficacy, poorly tolerated regimens, and non-compliance/non-persistence with antihypertensive treatment, which can be partly attributed to complex, multi-drug regimens[11].

Hypertension guidelines acknowledge that most patients with hypertension require two or more antihypertensive agents targeting complementary mechanisms of action to control BP, and that SPCs aid treatment compliance[6,12,13]. Furthermore, guidelines indicate that a renin–angiotensin–aldosterone system blocker together with a calcium channel blocker and/or a diuretic are among the logical combinations[6,12].

Much clinical evidence has been accumulated from randomized controlled trials demonstrating the BP-lowering efficacy and tolerability of amlodipine/valsartan (Aml/Val) and amlodipine/valsartan/hydrochlorothiazide (Aml/Val/HCT) combination therapies in patients with hypertension[14–20]. However, after efficacy has been demonstrated under controlled trial conditions, there is a need to collect data from larger patient populations in order to gain a better understanding of the effectiveness and tolerability of antihypertensive treatments used in routine clinical practice. These studies can include patients who have a broad range of baseline characteristics; a more heterogeneous population than is sometimes included in a single randomized controlled trial, and, as such, can represent the variety of patients encountered in clinical practice. Specifically, real-world data on the clinical effectiveness and tolerability of Aml/Val and particularly Aml/Val/HCT SPC therapies in developing economies is limited.

The real-world clinical EXperienCe of amlodIpine and valsarTan in hypErtension (EXCITE) study assessed the effectiveness, safety and tolerability of Aml/Val and Aml/Val/HCT, and adherence to these SPC therapies over a period of approximately 26 weeks in patients with arterial hypertension treated in routine clinical practice at centers in the Middle East and Asia. The study also aimed to make these assessments across a range of patient subgroups, reflecting different patient characteristics, risk-factor profiles and treatment dosages.

Methods

This was a prospective, multinational, multicenter, post-authorization study, conducted in countries in the Middle East (Bahrain, Egypt, Kuwait, Lebanon, Oman, Qatar, and United Arab Emirates) and Asia (Indonesia, Hong Kong, Pakistan, Philippines, South Korea, and Taiwan) between June 2010 and November 2012. It was conducted as a non-interventional study, in accordance with the definition applied by the European Medicines Agency (Directive 2001/20/EC). As such, study-specific patient visits, tests and monitoring were not imposed, and only data originating from routine clinical practice were collected. Therapy was prescribed according to clinician preference and clinical indication based on the prescribing information in the respective countries, and was clearly separated from the decision to include the patient in the study.

Study participants

Adults (aged ≥18 years) with an established diagnosis of hypertension, for whom SPC treatment with Aml/Val or Aml/Val/HCT had been prescribed by a treating physician as part of routine patient care, and who consented to data collection, were eligible for inclusion in the study. Aml/Val or Aml/Val/HCT was administered as single therapy or as add-on therapy to diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The following drug dosages (prescribed in accordance with local prescribing information) were studied: Aml/Val at 5/80 mg, 5/160 mg, 10/160 mg, 5/320 mg or 10/320 mg, and Aml/Val/HCT at 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg or 10/320/25 mg. Patients were excluded from the study if they had any contraindication to Aml/Val or Aml/Val/HCT as defined in the local prescribing information for their country.

The study was performed according to national requirements and regulations for the conduct of

non-interventional studies. Written informed consent for the collection and use of data was obtained from all participants. Patients were discontinued from the study if they withdrew informed consent or they were no longer taking Aml/Val or Aml/Val/HCT. During the observational period of approximately 26 ± 8 weeks, data from at least two routine patient visits were recorded: the baseline visit and a final visit at the end of the study. In addition, the treating physician could record data from an optional visit performed approximately 13 weeks after initiation of the study.

Outcome assessments

The primary efficacy endpoint was change from baseline to final visit (at 26 ± 8 weeks) in mean sitting systolic BP (msSBP) and mean sitting diastolic BP (msDBP). The change from baseline in msSBP and msDBP was additionally evaluated in subgroups of patients based on baseline msSBP: 140 to <160 mmHg, 160 to <180 mmHg, and ≥180 mmHg. Effectiveness for BP reduction was also assessed according to the proportion of patients who achieved therapeutic goal BP, defined as systolic BP (SBP) <140 mmHg and diastolic BP (DBP) <90 mmHg (or SBP <130 mmHg and DBP <80 mmHg in patients with co-morbid diabetes), and the proportion of patients achieving a BP response. SBP response was defined as SBP <140 mmHg (<130 mmHg in patients with diabetes) or a reduction of ≥20 mmHg, and DBP response was defined as DBP <90 mmHg (<80 mmHg in patients with diabetes) or a reduction of ≥10 mmHg. At the end of the study, a subjective assessment of treatment adherence, effectiveness and tolerability was made by the treating physician.

Safety and tolerability were assessed by physician monitoring of adverse events (AEs) and serious AEs (SAEs) and assessment of the incidence and intensity of edema.

Statistical analysis

Data from one umbrella protocol were pooled for analysis from 13 countries (Bahrain, Egypt, Hong Kong, Indonesia, Kuwait, Lebanon, Oman, Pakistan, Philippines, Qatar, South Korea, Taiwan and United Arab Emirates). Patients from Saudi Arabia were excluded from this analysis due to non-compliance with the study protocol. Safety data from this country are the subject of a separate report. Results from each country protocol will also be reported on an individual basis, in addition to the current pooled analysis. All effectiveness and safety analyses were performed on the full analysis set, consisting of patients who provided informed consent and entered the study. Continuous variables were summarized using the number of valid observations, mean, standard deviation (SD), median, minimum, and maximum. Frequency and percentage are presented for categorical variables. Confidence intervals (CIs) were provided to inform on the size of the treatment differences found.

The aim of the effectiveness analyses was to compare BP endpoints before and after treatment. A paired *t*-test was used to assess the change in BP from baseline to end of study. For patients who discontinued before the final visit (week 26 ± 8), the last available post-baseline value was carried forward (last observation carried forward; LOCF). Changes from baseline were analyzed separately by treatment cohort and dosage group. The incidence of AEs and SAEs were summarized with frequency counts and percentages by primary system organ class and preferred term in each cohort. Data analysis was performed by Biometrical Practice AG, Basel, Switzerland, using the SAS statistical package version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics and baseline characteristics

Of the 9794 patients enrolled and analyzed, 8603 (87.8%) received Aml/Val and 1191 (12.2%) received Aml/Val/HCT. Overall, 8081 patients (93.9%) in the Aml/Val treatment cohort and 1159 in the Aml/Val/HCT cohort (97.3%) completed the study. The main reason for premature study discontinuation was loss to follow-up (349 patients [3.6%]) (Table 1).

Patients included in the study were from the Middle East (Egypt, 26.2%; Lebanon, 20.7%; United Arab Emirates, 14.2%; Oman, 4.8%; Kuwait, 4.6%; Qatar, 3.5%; and Bahrain, 1.2%) and Asia (Philippines, 10.8%; Indonesia, 5.1%; Pakistan, 5.1%; Taiwan, 2.5%; South Korea, 1.1%; and Hong Kong, 0.3%). Patients were predominantly of Caucasian (47.2%) or Asian (41.4%) race. The mean age for the overall study population was 53.2 ± 11.4 years and there were slightly more male (60.6%) than female (39.4%) patients. The mean (±SD) duration of hypertension was 5.9 ± 6.5 years. Approximately one-third of patients (31.3%) had concomitant diabetes and one-third (32.5%) were classified as obese (body-mass index ≥30 kg/m^2) (Table 2). Overall, 25.5% patients were smokers, 46.6% had dyslipidemia, 42.5% had a family history of hypertension, 9.8% had coronary heart disease, 2.5% had experienced a previous myocardial infarction, 2.5% had a previous diagnosis of heart failure and 3.5% had experienced a previous cerebrovascular event. In addition, 6.7% of patients had microalbuminuria, 2.3% had elevated creatinine and 2.3% had chronic kidney disease; 19.8% had no pre-existing cardiovascular condition.

Table 1. Patient disposition.

n (%)	Aml/Val	Aml/Val/HCT	Total
Patients	8603	1191	9794
Completed the study	8081 (93.9)	1159 (97.3)	9240 (94.3)
Premature discontinuation	452 (5.3)	31 (2.6)	483 (4.9)
Data missing	70 (0.8)	1 (0.1)	71 (0.7)
Primary reason for premature discontinuation			
Death*	9 (0.1)	1 (0.1)	10 (0.1)
AE(s)	57 (0.7)	5 (0.4)	62 (0.6)
Abnormal laboratory value(s)	2 (<0.1)	0	2 (<0.1)
Unsatisfactory therapeutic effect	3 (<0.1)	0	3 (<0.1)
No longer requiring treatment	7 (0.1)	0	7 (0.1)
Withdrew consent	27 (0.3)	2 (0.2)	29 (0.3)
Lost to follow-up	327 (3.8)	22 (1.8)	349 (3.6)
Protocol deviation	13 (0.2)	0	13 (0.1)
Administrative problems	6 (0.1)	1 (0.1)	7 (0.1)
Data missing	1 (<0.1)	0	1 (<0.1)

AE, adverse event; Aml/Val, amlodipine/valsartan; Aml/Val/HCT, amlodipine/valsartan/hydrochlorothiazide.
Full analysis set.
*An additional three deaths were reported during the study, either as AEs or mentioned in the patient's narrative; all deaths reported during the study were considered to be unrelated to the medication of interest.

In the overall study population, most patients (77.1%) were receiving antihypertensive treatment prior to study entry. At baseline, the majority of patients (71.8%) were receiving Aml/Val or Aml/Val/HCT SPCs as the only treatment for hypertension. Overall, 16.9% of patients were receiving one additional antihypertensive medication at baseline (16.9% in the Aml/Val group and 16.3% in the Aml/Val/HCT group); 2.5% were receiving two additional antihypertensive medications (2.7% in the Aml/Val group and 1.3% in the Aml/Val/HCT group) and 0.4% were receiving three or more additional antihypertensive medications at baseline (0.5% in the Aml/Val group and 0.1% in the Aml/Val/HCT group).

BP reductions with Aml/Val and Aml/Val/HCT

For the primary study endpoint, there were significant decreases in msSBP and msDBP from baseline to study end in both the Aml/Val and Aml/Val/HCT treatment groups (Figure 1). Overall reductions in msSBP (95% CI) from baseline at study end were: −31.0 (−31.42, −30.67) mmHg in the Aml/Val group and −36.6 (−37.61, −35.50) mmHg in the Aml/Val/HCT group (Figure 1). Corresponding overall reductions in msDBP (95% CI) were −16.6 (−16.79, −16.34) mmHg in the Aml/Val group and −17.8 (−18.41, −17.22) mmHg in the Aml/Val/HCT group (Figure 1).

Significant decreases in baseline BP were observed in all dosage categories of Aml/Val and Aml/Val/HCT treatments and BP reductions were greater among patients receiving higher dosages (Figure 1). For patients completing the study (LOCF), msSBP/msDBP was 129.9/80.6 mmHg with Aml/Val and 129.3/79.9 mmHg with Aml/Val/HCT. Decreases in msSBP and msDBP at study end were greater in patients with more severe systolic hypertension (SBP ≥180 mmHg or between 160 and 180 mmHg) at baseline than those with milder forms of hypertension (Figure 2). For example, in patients with severe systolic hypertension (SBP ≥180 mmHg at baseline), reductions in msSBP of −53.6 and −55.7 mmHg and reductions in msDBP of −21.7 and −22.0 mmHg were observed for Aml/Val and Aml/Val/HCT groups, respectively, at study end.

BP goal attainment and response rates with Aml/Val and Aml/Val/HCT

Therapeutic BP goals were defined as SBP <140 mmHg and DBP <90 mmHg or, in patients with co-morbid diabetes, SBP <130 mmHg and DBP <80 mmHg at study end. The proportion of patients who reached BP goal at the final visit (LOCF) was 52.8% for Aml/Val and 54.5% for Aml/Val/HCT. BP response rates were defined as SBP <140 mmHg (<130 mmHg in patients with diabetes) or a reduction of ≥20 mmHg from baseline, and DBP <90 mmHg (<80 mmHg in patients with diabetes) or a reduction of ≥10 mmHg from baseline. The corresponding response rates for SBP and DBP were 86.9% and 89.2% with Aml/Val, and 89.2% and 88.9% with Aml/Val/HCT, respectively. BP response rates and the proportions of patients achieving therapeutic goal were consistent at these levels across different Aml/Val and Aml/Val/HCT dosage groups (data not shown), except in the 10/320 mg Aml/Val dosage group, where a slightly lower proportion of patients achieved therapeutic goal (30.8%). The proportion of all patients with and without diabetes who reached the therapeutic BP goal of <140/90 mmHg at the final visit (LOCF) was 69.9% with Aml/Val and 70.9% with Aml/Val/HCT. The corresponding SBP and DBP response rates for this analysis were 89.5% and 91.8% with Aml/Val and 91.0% and 91.4% with Aml/Val/HCT, respectively.

At week 13, 1033 patients (10.5%) had made a change to their antihypertensive therapy since the previous visit and 739 patients (7.5%) had changed their medication from week 13 to week 26. The most common reason given for any change in antihypertensive medication was unsatisfactory BP control (75.7% and 67.1% of patients at weeks 13 and 26, respectively). A small proportion of patients switched their SPC therapy (either the dosage or treatment group) during the study: 344 (3.9%) of patients receiving Aml/Val treatment switched to triple

Table 2. Patient demographics and baseline clinical characteristics.

Variable	Aml/Val ($n=8603$)	Aml/Val/HCT ($n=1191$)	Total ($n=9794$)
Age, years	52.8 ± 11.32	56.0 ± 11.15	53.2 ± 11.35
Age ≥65 years, *n* (%)[a]	1239 (14.4)	280 (23.5)	1519 (15.5)
Male[b]	5228 (60.8)	704 (59.1)	5932 (60.6)
Race, *n* (%)[c]			
Caucasian	3996 (46.4)	627 (52.6)	4623 (47.2)
Black	139 (1.6)	34 (2.9)	173 (1.8)
Asian	3618 (42.1)	432 (36.3)	4050 (41.4)
Other[d]	850 (9.9)	98 (8.2)	948 (9.7)
BMI ≥30 kg/m^2, *n* (%)[e]	2766 (32.2)	418 (35.1)	3184 (32.5)
Diabetes, *n* (%)[f]	2663 (31.0)	400 (33.6)	3063 (31.3)
Duration of hypertension, years	5.8 ± 6.5	6.5 ± 6.7	5.9 ± 6.5
Prior antihypertensive treatment, *n* (%)[g]	6548 (76.1)	1008 (84.6)	7556 (77.1)
Baseline BP, mmHg			
msSBP	160.8	166.0	
msDBP	97.0	97.7	

Aml/Val, amlodipine/valsartan; Aml/Val/HCT, amlodipine/valsartan/hydrochlorothiazide; BMI, body mass index; BP, blood pressure; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure.
Full analysis set. Values are mean ± standard deviation unless otherwise stated.
[a]Age data missing for 47 patients.
[b]Gender data missing for one patient.
[c]Race data missing for nine patients.
[d]Including Native American and Pacific Islander.
[e]BMI data missing for 708 patients.
[f]Cardiovascular risk factor data missing for 25 patients.
[g]Prior antihypertensive treatment data missing for 27 patients.

therapy with Aml/Val/HCT and 31 (2.6%) of patients in the Aml/Val/HCT group switched to Aml/Val.

Safety and tolerability

Aml/Val and Aml/Val/HCT SPCs were generally well tolerated. AEs were reported in 963 patients (11.2%) in the Aml/Val group and 73 patients (6.1%) in the Aml/Val/HCT group (Table 3). The most common AEs reported in the Aml/Val and Aml/Val/HCT groups were edema and peripheral edema (Table 3). Most of the AEs reported in the Aml/Val and Aml/Val/HCT groups were assessed as being unrelated to the medication of interest by study investigators.

The overall rate of SAEs was low (50 patients; 0.5%; Aml/Val: $n=49$ [0.6%], Aml/Val/HCT: $n=1$ [0.1%]). The most frequent SAEs were cardiac disorders, occurring in 23 patients in the Aml/Val group (0.3%) and none in the Aml/Val/HCT group. Most of the SAEs reported in Aml/Val and Aml/Val/HCT groups were assessed as being unrelated to the medication of interest according to study investigators. Thirteen deaths were reported during the study, none of which were considered by investigators to be related to the medication of interest.

Physicians' assessments

Effectiveness of treatment was rated as 'good' or 'very good' in the majority of patients (Aml/Val: 87.7%, Aml/Val/HCT: 94.7%), while tolerability was assessed as 'good' or 'very good' in 89.5% of patients in the Aml/Val group and 96.0% of patients in the Aml/Val/HCT group. Treatment adherence was also rated as 'good' or 'very good' for most patients in each treatment group (Aml/Val: 89.6%, Aml/Val/HCT: 95.8%). Effectiveness, tolerability and adherence were assessed as 'good' or 'very good' in a slightly larger proportion of patients receiving Aml/Val/HCT than Aml/Val.

Discussion

This is a large prospective study of Aml/Val and Aml/Val/HCT SPC antihypertensive therapy carried out on patients with hypertension in a real-world setting. A cohort of >9700 patients with hypertension from 13 countries in the Middle East and Asia were observed in routine clinical practice. The results demonstrated that both Aml/Val and Aml/Val/HCT provided statistically significant and clinically relevant reductions in msSBP and msDBP from baseline over the study period; thus confirming the effectiveness of both dual SPC therapy with Aml/Val and triple SPC therapy with Aml/Val/HCT for BP reduction in a diverse, multi-ethnic patient population with hypertension from the Middle East and Asia.

Overall, more than half of all patients in the study reached the pre-defined therapeutic BP goal and the majority of patients also attained a BP response with

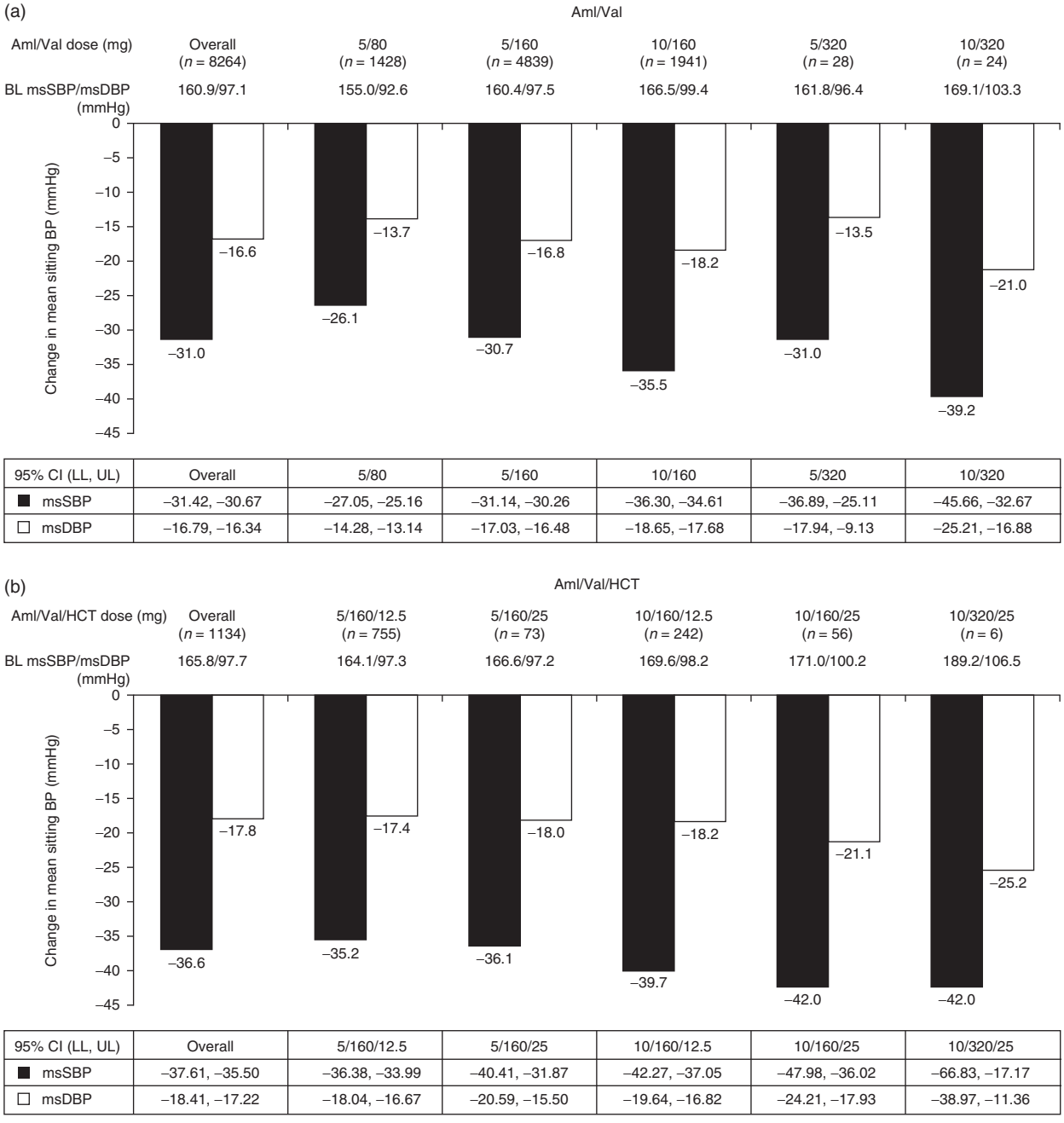

Figure 1. Mean change from baseline to week 26* in msSBP and msDBP according to dosage in patients treated with (a) Aml/Val and (b) Aml/Val/HCT. Aml/Val, amlodipine/valsartan; Aml/Val/HCT, amlodipine/valsartan/hydrochlorothiazide; BL, baseline; BP, blood pressure; CI, confidence interval; LL, lower limit; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure; UL, upper limit. Full analysis set. *Last observation carried forward.

Aml/Val and Aml/Val/HCT therapies. As expected, the magnitude of reductions in BP increased (from a varying baseline BP value) as the dose of each antihypertensive increased, and were also proportional to baseline hypertension severity, with the largest BP reductions reported in patients with SBP ≥180 mmHg at baseline. Both SPCs were also generally well tolerated in this patient population, with low overall rates of edema and other AEs reported in the study.

Accepting inherent differences in the study design and methodology compared with other clinical trials with Aml/Val and Aml/Val/HCT in patients with hypertension, these results appear to be generally consistent with previous studies reporting clinically meaningful BP

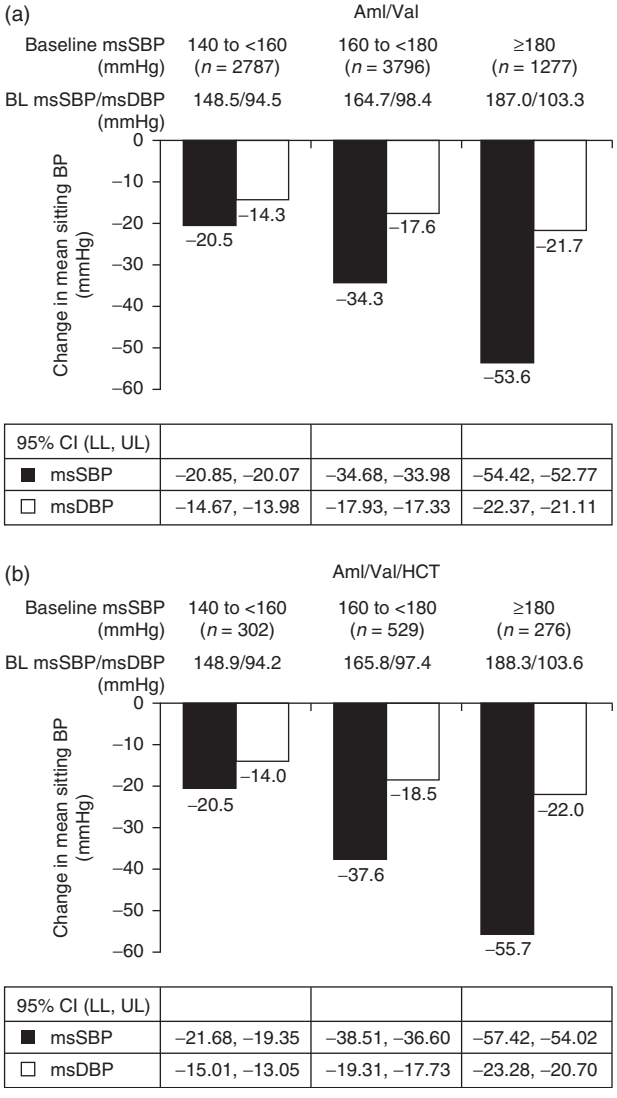

Figure 2. Overall mean change from baseline to week 26* in msSBP and msDBP according to severity of hypertension in (a) Aml/Val cohort or (b) Aml/Val/HCT cohort. Aml/Val, amlodipine/valsartan; Aml/Val/HCT, amlodipine/valsartan/hydrochlorothiazide; BL, baseline; BP, blood pressure; CI, confidence interval; LL, lower limit; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure; UL, upper limit. Full analysis set. *Last observation carried forward.

lowering across all Aml/Val and Aml/Val/HCT dosages and severities of hypertension[15,16,20–22]. In particular, results from the EXCITE study also appear to be generally in line with those reported in two other real-world studies of patients with hypertension receiving Aml and Val. In the first of these, 2729 patients from Asia, Egypt and Russia (baseline BP 163.1/96.2 mmHg) received a free combination of Aml and Val. BP at the end of the 12 week treatment period was 129.9/79.3 mmHg[21], similar to the end-of-study BP of 129.9/80.6 mmHg achieved by patients in the Aml/Val group of the current study. Similarly, in another 12 week real-world study of

Table 3. Most frequently reported AEs.

n (%)	Aml/Val (*n* = 8603)	Aml/Val/HCT (*n* = 1191)	Total (*n* = 9794)
Total AEs	963 (11.2)	73 (6.1)	1036 (10.6)
Edema	173 (2.0)	39 (3.3)	212 (2.2)
Peripheral edema	99 (1.2)	9 (0.8)	108 (1.1)
Headache	87 (1.0)	2 (0.2)	89 (0.9)
Cough	52 (0.6)	3 (0.3)	55 (0.6)
Nausea	41 (0.5)	2 (0.2)	43 (0.4)
Dizziness	38 (0.4)	0	38 (0.4)
Bronchitis	33 (0.4)	0	33 (0.3)
Gastritis	28 (0.3)	0	28 (0.3)
Dyslipidemia	24 (0.3)	1 (0.1)	25 (0.3)
Vomiting	23 (0.3)	0	23 (0.2)

AE, adverse event; Aml/Val, amlodipine/valsartan; Aml/Val/HCT, amlodipine/valsartan/hydrochlorothiazide.
Events occurring in ≥0.3% of any treatment group.
Full analysis set.

Aml/Val (5/80, 5/160 or 10/160 mg) with 8336 patients (the largest group of patients were from Russia), mean SBP/DBP was reduced from 165.0/99.3 mmHg at baseline to 128.7/80.4 mmHg at study end (−36.3/−18.9 mmHg)[22].

Achievement of BP targets remains an elusive goal for many of those receiving antihypertensive therapy[10]. Data from the EXCITE study show that, in a large, multi-ethnic population, more than half of all patients achieved the pre-defined therapeutic BP goal, and an even higher proportion achieved a pre-defined BP response (>87%). In this analysis, patients with diabetes were required to reach a lower pre-defined BP target of <130/80 mmHg. It is acknowledged that achieving such rigorous BP goals in these high-risk and difficult-to-treat patients can be challenging[23,24]. The value of setting more aggressive BP targets for these types of patients has recently been debated in the literature, and some hypertension guidelines have recognized that a BP goal closer to the conventional target BP may be more appropriate, even for patients with diabetes[12,25,26]. In this regard, an analysis was carried out on all patients from the EXCITE study (including patients with diabetes) who achieved the SBP/DBP goal of <140/90 mmHg. In this analysis, the proportion of patients achieving therapeutic goal was approximately 70% (69.9% in the Aml/Val group and 70.9% in the Aml/Val/HCT group), with approximately 90% achieving individual SBP/DBP responses in both the Aml/Val and Aml/Val/HCT groups.

Aml/Val and Aml/Val/HCT were well tolerated in this diverse patient population. Tolerability was rated as 'good' or 'very good' in 89.5% of patients in the Aml/Val group and 96.0% in the Aml/Val/HCT group and the incidence of AEs was 11.2% and 6.1% in the Aml/Val and Aml/Val/HCT groups, respectively. As expected, edema and peripheral edema were the most frequently reported AEs in the Aml/Val and Aml/Val/HCT treatment groups. Most of the AEs and SAEs reported in the Aml/Val and Aml/Val/

HCT groups were assessed as being unrelated to the medications of interest. No deaths were reported as being related to the medications of interest.

Poor adherence to antihypertensive therapy is another potential reason why patients may not achieve BP goals[11]. Studies have reported that patients adherent to antihypertensive therapy are more likely to achieve target BPs[27], have a lower risk of cardiovascular events[28,29] and hospitalization[30], and have lower overall healthcare costs[30], compared with those who do not adhere to therapy. In the EXCITE study, subjective, investigator-rated adherence was assessed as 'good' or 'very good' for the majority of patients (89.6% in the Aml/Val group and 95.8% in the Aml/Val/HCT group).

The non-randomized, open-label design of this study is one of its inherent limitations, as this can introduce the potential for observer bias due to the lack of blinding and the absence of standardized methods for data collection. However, the observational design of the study has permitted the collection of a large amount of real-world data from an extensive, heterogeneous patient population with hypertension, which is arguably more representative of the patient population encountered in routine clinical practice. It is reassuring to note that the main findings from this real-world study, including reductions in BP with Aml/Val and Aml/Val/HCT across different dosages and different severities of hypertension, are generally in line with previous studies[15,16,20–22]. By analyzing data pooled from 13 countries, the EXCITE study has contributed a significant body of data on the management of hypertension with Aml/Val and particularly Aml/Val/HCT (for which comparatively less data are available). It has also permitted collection of data from a wide range of patients, including those from developing economies who face an increasing hypertension burden. Notably, useful data have been collected for a number of countries in the Middle East and Asia for which research on antihypertensive treatment has been limited. The large number of patients included also serves to increase the validity of the data, as indicated by the narrow CIs for the main study outcomes.

In addition, a further limitation of this study is the use of subjective evaluation scales for the investigator assessment of effectiveness, tolerability and treatment compliance. While not as robust as objective measures of adherence to therapy, it is still useful to have some indication of the levels of patient adherence achieved in routine clinical practice as this is difficult to assess in the highly regulated environment of a clinical trial.

Conclusions

In this large cohort of patients with hypertension from the Middle East and Asia, SPC treatment with Aml/Val or Aml/Val/HCT provided statistically significant and clinically relevant reductions in BP from baseline across all treatment dosages and severities of hypertension in a real-world setting. Both SPCs were generally well tolerated in this patient population.

Transparency

Declaration of funding

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Declaration of financial/other relationships

J.S., S.H.A.-K., R.N., A.R.K., B.C. and K.-C.U. have disclosed that they received investigator fees related to the conduct of the EXCITE study from Novartis and its affiliates. A.S. has disclosed that he is an employee and shareholder of Novartis Pharma AG. D.K. has disclosed that she is an employee of Novartis Pharma AG.

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