Clinical Effectiveness, Safety and Tolerability of Amlodipine/Valsartan in Hypertensive Patients: the Indonesian Subset of the EXCITE Study

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ABSTRAK

Tujuan: *menilai keefektifan, keamanan dan tolerabilitas kombinasi tetap amlodipine/valsartan (Aml/Val) pada pasien hipertensi dalam praktek klinik sehari-hari.* ***Metode:*** *subset Indonesia dari studi EXCITE (clinical EXperienCe of amlodIpine and valsarTan in hypertEnsion), yang merupakan studi terbuka, observasional, prospektif dan multinasional pada pasien hipertensi yang diobati dengan kombinasi tetap Aml/Val selama 26 minggu. Kombinasi tetap Aml/Val 5/80, 5/160 atau 10/160 mg diberikan sebagai obat monoterapi atau ditambahkan pada obat antihipertensi lain pada pasien yang tidak terkontrol oleh monoterapi sebelumnya. Outcome keefektifan yang diukur adalah (1) rata-rata penurunan TDS (tekanan darah sistolik) dan TDD (tekanan darah diastolik) duduk dari awal terapi ke minggu 26; (2) proporsi pasien yang mencapai kontrol TD (<140/90 mmHg pada pasien bukan diabetes atau <130/80 mmHg pada pasien diabetes); (3) proporsi pasien yang merupakan responder (mencapai kontrol TD atau penurunan TD >20/10 mmHg). Outcome keamanan yang diukur adalah insidens kejadian tidak diinginkan (KTD) dan KTD serius (KTDS), dan insidens edema.* ***Hasil:*** *total 500 pasien dari Indonesia mendapat kombinasi tetap Aml/Val, 487 pasien dianalisis untuk efikasi, dan 464 pasien menyelesaikan studi. Pada akhir studi (minggu 26), rata-rata penurunan TDS dan TDD duduk (95% CI) dari awal terapi adalah -33,7 (-35,2 → -32,1) mmHg dan -14,8 (-15,7 → -13,8) mmHg. Di antara 487 pasien ini, 52,4% pasien mencapai kontrol TD dan 80,5% pasien adalah responder (LOCF). Di antara 464 pasien yang menyelesaikan studi, 53,7% pasien mencapai kontrol TD dan 84,5% pasien adalah responder. Kombinasi tetap Aml/Val efektif dalam menurunkan TD pada pasien Indonesia. Total pasien dengan KTD, termasuk KTDS, adalah 11,4%, 1% dengan KTDS, dan 0,8% pasien meninggal. KTDS dan kematian diperkirakan tidak berhubungan dengan obat studi. Edema dilaporkan oleh 9,4% pasien pada awal studi dan 3,7% pada akhir studi. Peneliti menilai bahwa keefektifan obat, serta tolerabilitas dan kepatuhan pasien, baik dan sangat baik pada 90,8%, 92,2% dan 89,2% pasien berturut-turut.* ***Kesimpulan:*** *kombinasi tetap Aml/Val efektif dan ditoleransi dengan baik untuk menurunkan TD pada pasien hipertensi, yang tidak terkontrol dengan monoterapi, dalam praktek sehari-hari di Indonesia.*

ABSTRACT

Aim: *to assess the effectiveness, safety and tolerability of amlodipine/valsartan (Aml/Val) single-pill combination (SPC) in hypertensive patients in a real-world setting.* ***Methods:*** *the Indonesian subset of the EXCITE (clinical EXperience of amlodIpine and valsarTan in hypErtension) study, which was a multinational, prospective, observational, open study in hypertensive patients treated with Aml/Val SPC for 26 weeks. Aml/Val*

SPCs (5/80, 5/160, 10/160 mg) were administered as monotherapy or as add-on therapy to other antihypertensive medications in patients not controlled by prior monotherapy. The effectiveness outcomes were (1) mean decrease in sitting systolic blood pressure and diastolic blood pressure (msSBP and msDBP) from baseline to week 26; (2) proportion of patients achieving BP goal (<140/90 mmHg for nondiabetics, or <130/80 mmHg for diabetics); (3) proportion of patients who were responders (achieving BP goal or BP reduction of >20/10 mmHg). The safety variables were the incidence of AEs and SAEs, and the incidence of edema. ***Results:*** *a total of 500 patients from Indonesia received Aml/Val SPC, 487 patients were analyzed for efficacy (by LOCF), and 464 patients completed the study. At study end (week 26), the overall msSBP and msDBP(95% CI) reductions from baseline were -33.7 (-35.2, -32.1) mmHg and -14.8 (-15.7, -13.8) mmHg, respectively. Among the 487 patients, 52.4% achieved BP goal and 80.5% were responders (LOCF). Among 464 patients who completed the study, 53.7% achieved BP goal and 84.5% were responders. Aml/Val SPC was effective in decreasing BP in Indonesian patients. AEs, including SAEs, were reported in 11.4% patients, with SAEs in 1% of patients, and death in 0.8% of patients. SAEs and deaths were considered unrelated to the study drug. Edema was reported by 9.4% of patients at baseline, and in 3.7% patients at end of study. Effectiveness, tolerability and compliance were rated good and very good in 90.8%, 92.2%, and 89.2% of patients, respectively, according to the investigators.* ***Conclusion:*** *Aml/Val SPC was effective for BP reductions and well tolerated in hypertensive patients, not adequately controlled by monotherapy, in a daily clinical setting in Indonesia.*

Key words: *Aml/Val, single-pill combination, daily clinical, EXCITE study.*

INTRODUCTION

Hypertension is a common medical problem in developing countries, and rates of awareness, treatment, and control are generally low. More than 80% of the world population lives in developing countries, where most of the world burden of hypertension exists. By 2025, almost three-quarters of people with hypertension will be living in developing countries.[1] High illiteracy rates, poor access to health facilities, bad dietary habits, poverty, and high cost of drugs contribute to poor blood pressure control in these countries.[2]

The prevalence of hypertension among Indonesian adults (≥18 years) is 26.5-31.7%.[3,4] Those who are aware that they have the disease are 7.7-9.5%[3,4] and 2.3% take antihypertensive medication.[4]

Until now, there were only 4 published papers on antihypertensive treatments in Indonesia, one study was a bridging study of labetalol for hypertension in Indonesia[5], 2 studies were randomized clinical trials[6,7], and another study was a postmarketing observational study of candesartan and candesartan/HCT.[8] According to the clinical trials, achievement of BP control varied from 26.9% to 45%[5-7], while the postmarketing study showed BP control of 53% in patients, not adequately controlled by previous therapy.[8]

International guidelines recommend that most patients with hypertension will require more than one antihypertensive medication to achieve their BP goals. A combination of two drugs should be chosen from different classes, either as free or fixed combinations.[9,10] Combination of CCBs with ARBs are amongst the preferred ones.[10] Single pill combinations (SPC) of amlodipine/valsartan (Aml/Val) has been shown to be highly effective and well tolerated in randomized clinical trials with Caucasians[11-13,17], Asians[14,15,17], and Blacks.[16,17] However, clinical trial setting is a restricted one and therefore does not reflect the real-world situation.

We were interested in knowing the performance of Aml/Val SPC in a real-world setting in Indonesia. Real-life studies of Aml/Val combination have been conducted in many countries, including Asian and Middle-East countries, as multinational post-marketing studies (PMS).[18-20] Indonesia was included in one of these PMSs, i.e. the EXCITE study[20], although Indonesia has conducted its own study (the MAX-FORCE study).[21] China status II[22] was another observational study conducted

in China that was not part of a multinational one, just as MAX-FORCE in Indonesia. As a subset of the EXCITE study, the primary objective of the present study was similar to that of the EXCITE study, i.e. to assess the effectiveness, safety and tolerability of Aml/Val SPC therapies in hypertensive patients under routine clinical practice during 26 weeks of treatment. The secondary objectives were to evaluate patient adherence to treatment and the incidence of edema. Due to the limited data on antihypertensive treatments in Indonesia, this study would become an important addition to it.

METHODS

Male and female outpatients, aged ≥18 years with essential hypertension not adequately controlled by previous antihypertensive medications, for whom treatment with SPC of Aml/Val was medically recommended as part of their medical care, were eligible for this study.

Patients with hypersensitivity to amlodipine, valsartan, or any of the excipients in the formulation, with severe renal impairment (creatinine clearance less than 10 ml/min) or severe hepatic impairment, with hereditary or history of angioedema, or any condition that according to the treating physicians prohibited participation in the study, were excluded. Pregnant women, nursing mothers, or women of child-bearing age without adequate contraception, were also excluded from this study.

Study Design and Procedure

The present study was the Indonesian subset of the EXCITE study. The EXCITE (clinical EXperienCe of amlodIpine and valsarTan in hypertEnsion) study was a multinational, multicenter, prospective, observational (non-interventional), open (non-comparative) study in hypertensive patients treated with a SPC of Aml/Val for 26 weeks (4 routine examinations: at baseline, week 4, week 13, and week 26). No intervention beyond usual care was applied to the patients.

The protocol and informed consent were approved by an appropriate ethics committee. The study commenced in March 2011 and ended in September 2012. It was conducted in Jakarta, Surabaya, Malang, Bandung, Semarang, Bali, and Makassar.

As a postmarketing study, without control group, with the primary objective "effectiveness, safety and tolerability", the sample size was determined without calculation (which is usually done for "efficacy" study), as many sample as possible were included but still affordable, usually between 500 and 1000 subjects. A total sample of 500 subjects were taken for this study.

Patient demographics and baseline characteristics were recorded at study entry, including: age, BMI, gender, race, ethnicity, duration of hypertension, risk factors, and other medical history including prior antihypertensive medications.

Aml/Val SPCs (5/80 mg, 5/160 mg, 10/160 mg) were administered as monotherapy or as add-on therapy to other antihypertensive medications. The hypertension therapy at study entry was recorded in the CRF (case report form). Any changes to medication during study participation were recorded in the CRF.

Outcome Assessments

The main effectiveness outcomes were (1) change in mean sitting SBP and DBP (msSBP and msDBP) from baseline to week 26; (2) the proportion of patients achieving BP goal (<140/90 mmHg for non-diabetics, or <130/80 mmHg for diabetics); (3) the proportion of patients who were responders (achieving BP goal or BP reduction of >20/10 mmHg).

Patients were requested to sit for at least 5 minutes prior to BP measurement. BP was measured using mercury sphygmomanometer that has been calibrated. Korotkoff phase 1 and phase 5 were taken as SPB and DBP. BP was measured twice and the mean value was taken.

The safety variables were the incidence of adverse events (AEs) and serious adverse events (SAEs), and the incidence of edema.

Statistical Analysis

Effectiveness and safety analyses were performed using both FAS (Full Analysis Set) population (LOCF method) and PP (Per Protocol) population.

Data analyses were performed using

descriptive statistics for demographics and baseline characteristics, and for safety evaluation. For effectiveness, the decreases in BP from baseline to study end were analyzed using paired-t test (the decreases in BP should be normally distributed), and the 95% CIs (confidence intervals) of the BP decreases were calculated.

RESULTS

Patient Demographics and Baseline Characteristics

All 500 patients (from Indonesia) received Aml/Val SPC. Thirty five patients (7%) discontinued early, the most common reason was lost to follow-up (24 patients, 4.8%), followed by death (4 patients, 0.8%). Three patients (0.6%) discontinued because the study drug was no longer required, 2 patients (0.4%) due to adverse events and 2 patients (0.4%) withdrew consent. For one patient, demographic information was not collected. The remaining 464 patients (92.8%) completed the study (26 weeks).

Demographics and baseline characteristics of patients are shown in **Table 1**.

All patients received previous antihypertensive medications, which were primarily dihydropyridines (45.4%).

The most common reason for changing treatment was unsatisfactory BP control during prior treatment in 366 patients (73.2%), followed by insufficient compliance and insufficient tolerability with prior treatment in 141 patients (28.2%) and 86 patients (17.2%), respectively.

At baseline, concomitant antihypertensive medications were used in 46 patients (9.2%), 1 drug in 39 patients (7.8%), and 2 drugs in 7 patients (1.4%), mostly β-blockers in 22 patients (4.4%), followed by thiazides in 16 patients (3.2%). By end of study (week 26), 51 patients (10.2%) used concomitant antihypertensives, 1 drug in 41 patients (8.2%), and 2 drugs in 10 patients (2.0%), β-blockers were the most prevalent, used in 33 patients (6.6%), followed by thiazides in 7 patients (1.4%).

Table 1. Patient demographics and baseline characteristics

Variables	Aml/Val (N = 500)
Age (years), mean (SD)	55.8 (11.01)
Age >65 years, n (%)	102 (20.4)
Male, n (%)	273 (54.6)
Race, n (%)	
- Asia	489 (97.8)
- Other	11 (2.2)
Ethnicity, n(%)	
- Chinese	156 (31.2)
- Other	344 (68.8)
BMI status (kg/m2), n (%)	
- <25	198(39.6)
- 25 – 30	227 (45.4)
- >30	65 (13.0)
- missing	10 (2.0)
Duration of hypertention (yrs), mean (SD)	5.8 (6.72)
Cardiovascular risk factor, n (%)	
- None	94 (18.8)
- Family history of HT	172 (34.4)
- Dyslipidemia	213 (42.6)
- Diabetes mellitus	138 (27.6)
- Obesity	105 (21.0)
- Smoking	60 (12.0)
- Creatinine increase	30 (6.0)
- Coronary heart disease	21 (4.2)
- Myocardial infarction	6 (1.2)
- Heart failure	4 (0.8)
Previous antihypertensive medications, n (%)	
- Dihydropyridines	227 (45.4)
- ACE inhibitors	114(22.8)
- ARBs	97(19.4)
- β-blockers	32(6.4)
- Thiazides	23 (4.6)

BP Reductions, Therapeutic Goal Attainment and Responders

By FAS (Full Analysis Set, N=487, because 13 patients had only baseline BP), mean sitting blood pressure (msBP) decreased from 164.1/96.4 mmHg at baseline to 130.5/81.6 mmHg at week 26 ($p<0.001$) (**Figure 1**). The decreases in msSBP and msDBP (95% CI) were -33.7 (-35.2, -32.1) mmHg and -14.8 (-15.7, -13.8) mmHg, respectively (**Figure 2**). The therapeutic goal (BP <140/90 mmHg for non-diabetics, or <130/80 mmHg for diabetics) was achieved by 255 patients (52.4%), and 80.5% were responders.

The therapeutic goal independent of diabetic status (BP<140/90 mm Hg) was achieved by 306 patients (62.8%).

Among the study completers (464 patients), msBP decreased from 164.3/96.4 mmHg at baseline to 130.3/81.5 mmHg at week 26, the decreases (95% CI) were -34.0 (-35.5, -32.4) mmHg and -14.9 (-15.85, -13.95) mmHg for msSBP and msDBP, respectively. The therapeutic goal was achieved by 249 patients (53.7%) and 392 patients (84.5%) were responders.

By treatment dosage, the reductions in msSBP and msDBP from baseline to study end are shown in **Figure 2**. The therapeutic goal was achieved by 183 patients (54.8%), 55 patients (58.5%), and 17 patients (29.3%) for dosages of 5/80, 5/160, and 10/160 mg, respectively.

Figure 3 shows mean BP reductions in subgroups of various baseline SBP after 26 weeks of treatment. The higher the baseline SBP, the greater the reductions in msSBP and msDBP at end of study.

Mean sBP reductions at end of study in patients with ISH or elderly at baseline and in DM or obese patients are shown in **Figure 4**.

Safety and Tolerability

A total of 57 patients (11.4%) reported at least one adverse event, including 5 patients (1%) with serious adverse events. Excluding edema (**Table 3**), the most frequent adverse event was dyslipidemia in 13 patients (2.6%), followed by cough in 9 patients (1.8%), and headache in 7 patients (1.4%) (**Table 2**).

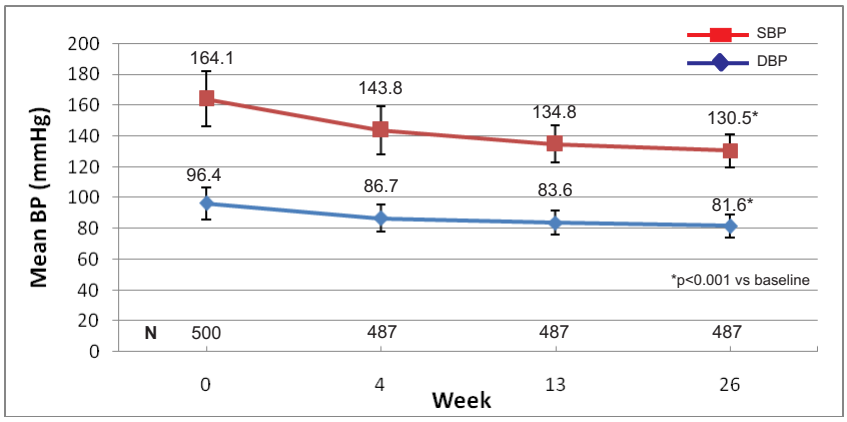

Figure 1. Mean sitting SBP and DBP during the study (last observation carried forward/LOCF) with Aml/Val SPC. Error bars represent SDs (standard deviations).

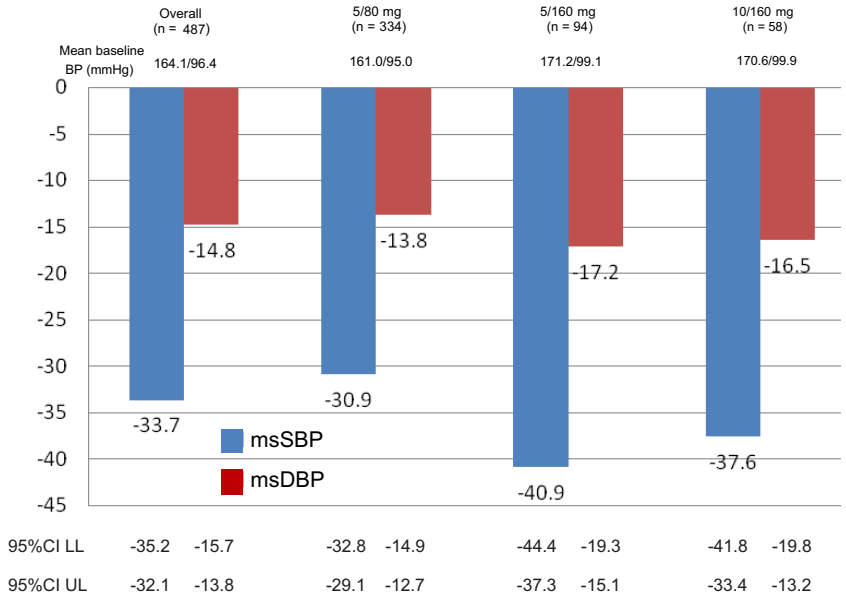

Figure 2. Mean sitting BP reductions at end of study (last observation carried forward/LOCF) in various Aml/Val dosage groups

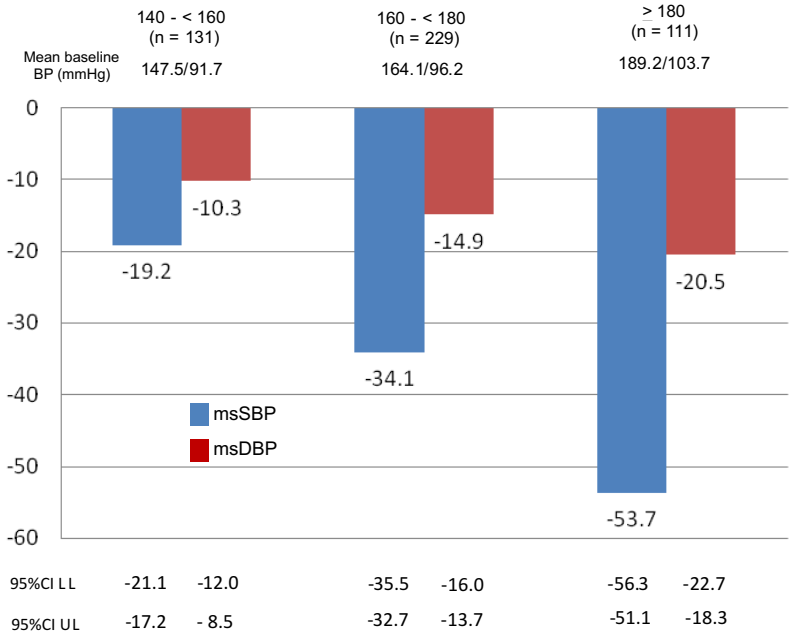

Figure 3. Mean sitting BP reductions at end of study (last observation carried forward/LOCF) in patients with various values of baseline SBP

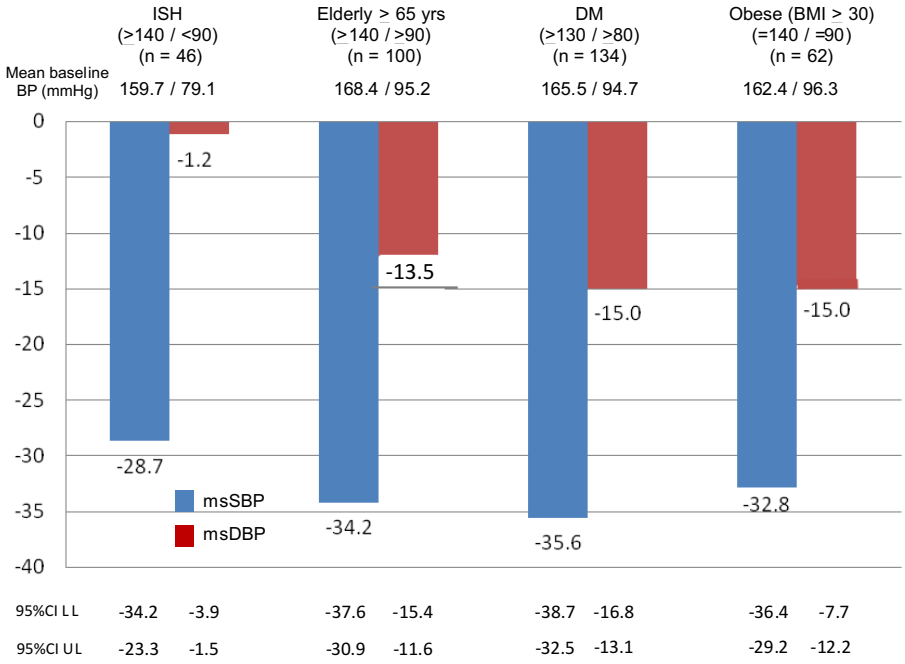

Figure 4. Mean BP reductions at end of study (last observation carried forward/LOCF) in various subgroups of patients: isolated systolic hypertension (ISH), elderly, DM, and obese

Among 5 patients with SAEs, 4 died out of which, one patient experienced a non-hemorrhagic stroke on study day 118, and 3 patients experienced myocardial infarction on study days 30, 92, and 140. None of these 4 deaths were suspected to be related to the study drug. One other patient reported nonfatal SAEs (dyspnea, insomnia, edema), also not suspected to be related to the study drug.

At baseline, there were 47 patients (9.4%) with edema, among them, 28 had received dihydropyridines as the previous antihypertensives. At end of study (week 26), total patients with edema decreased to 17 (3.7%).

Table 2. Patients with AEs, including SAEs (full analysis set, N=500)

	Aml/Val (N=500) n (%)
Total patients with AEs, including SAEs	57 (11.4)
- Dyslipidemia	13 (2.6)
- Cough	9 (1.8)
- Headache	7 (1.4)
- Diabetes mellitus	4 (0.8)
- Gastritis	4 (0.8)
- Rhinitis	4 (0.8)
- Hyperuricemia	3 (0.6)
- Myocardial infarction	3 (0.6)
- Pharyngitis	3 (0.6)
- Dyspepsia	2 (0.4)
- Dyspnea	2 (0.4)
- Inflammation	2 (0.4)
- Myalgia	2 (0.4)

Note: one patient may experience more than one AE

By treatment dosage, among 47 patients with edema at baseline, 36 patients received Aml/Val 5/80 mg, 5 patients received Aml/Val 5/160 mg, and 6 patients received Aml/Val 10/160 mg. At study end, among the remaining 17 patients with edema, there were 10 patients in the Aml/Val 5/80 mg group, 2 patients in the Aml/Val 5/160 mg group, and 5 patients in the Aml/Val 10/160 mg group (**Table 3**).

Investigators' Assessments

At the end of study, effectiveness, tolerability and compliance with treatment were assessed by the investigators (**Table 4**).

It was shown that effectiveness, tolerability, and compliance were rated good and very good in 90.8%, 92.2%, and 89.2% of patients, respectively, by the Investigators.

DISCUSSION

This was the Indonesian subset of the EXCITE study, which was a multinational, multicenter, prospective, postmarketing study in hypertensive patients treated with Aml/Val in a real-world setting. This study was very similar to a study conducted about one year earlier in Indonesia, the MAX-FORCE study.[21] The complete EXCITE study included patients from

Table 3. Edema by visit and treatment dosage: n (%)

Timepoint	Total N=500	5/80 mg N=339	5/160 mg N=97	10/160 mg N=63
Baseline	500 (100)	339	97	63
Total with edema	47 (9.4)	36	5	6
Mild	41 (8.2)	33	5	3
Moderate	4 (0.8)	2	-	2
Severe	2 (0.4)	1	-	1
End of study	464 (100)	321	92	50
Total with edema	17 (3.7)	10	2	5
Mild	14 (3.0)	8	1	5
Moderate	3 (0.6)	2	1	-
Severe	-	-	-	-

Table 4. Effectiveness, tolerability, and compliance with treatment at end of study: n (%)

	Effectiveness	Tolerability	Compliance
Total	500 (100)	500 (100)	500 (100)
Good	306 (61.2)	306 (61.2)	286 (57.2)
Very good	148 (29.6)	155 (31.0)	160 (32.0)
Would continue Aml/Val			455 (91.0)

Middle East countries as the majority, besides patients from Asian countries.[20]

The overall EXCITE study included about 9800 patients, compared to the Indonesian subset study, it had more males (61 vs 55%), a little bit younger age (mean age 53 vs 56 years), and 94 vs 93% completed the study.20 The premature discontinuation was also mainly due to lost to follow up (4 vs 7%).[20] The MAX-FORCE study recruited 488 patients, with similar age and similar percentage of males with the present study, and also similar percentage of patients who completed the study (for only 12 weeks duration).[21]

The previous antihypertensive medications, in the present study were primarily dihydropyridines, followed by ACE inhibitors, ARBs, and β-blockers. The same order of previous antihypertensive medications was found in the overall EXCITE study and in the MAX-FORCE study.[21]

The decrease in mean BP in this subset of EXCITE study (last observation carried forward/LOCF) was similar to the overall EXCITE

study, i.e. -33.7/-14.8 vs -31.0/-16.6 mmHg. The percentage of patients achieving therapeutic goal (BP <140/90 mmHg for nondiabetics or <130/80 mmHg for diabetics) was also similar (52.4 vs 52.8%).

Recent guidelines for the management of hypertension[23,24] mention that BP therapeutic goal for diabetics is <140/90 mm Hg. In this regard, the proportion of patients reaching therapeutic goal in the present study was 62.8%, which was comparable to the overall EXCITE study; 69.9%. In the MAX-FORCE study, the mean BP reductions from baseline to study end were -36.6/-16.4 mmHg, 62.4% achieved therapeutic goal (<140/90 mm Hg). These results showed that Aml/Val SPC has comparable efficacy in reducing BP in the present subset with the overall EXCITE study, and with the MAX-FORCE study as well.

The decrease in BP was proportional to the baseline: smallest decrease in the lowest baseline SBP, and greatest decrease in the highest baseline SBP (**Figure 3**). The same pattern of BP reduction was also shown in various grades of hypertensive patients (based on BP) in previous studies with Aml/Val SPC in real-world studies as well as in the main EXCITE study: the higher the grades of hypertension, the greater the decrease in BP.[18-22] This is because the efficacy of CCBs in lowering BP is proportional to the baseline BP.[25] This is also true for a combination of an ARB (irbesartan) and HCT.[26] The magnitude of BP reductions by ARBs is less dependent on the baseline BP than it is by CCBs.[27]

For study completers (N = 464), 53.7% achieved therapeutic goal. In Pakistan subset study[28], 471 patients (94%) received Aml/Val, and among the study completers (N=411), 237 patients (57.7%) achieved therapeutic goal, comparable to our study. Results in previous real-life studies showed that BP control (<140/90mmHg) was achieved by 75.6% from a total of 2729 patients[18], and by 77.7% from a total of 8336 patients[19], after 12 weeks of treatment with Aml/Val.

Compared with the results of LOCF analysis, the study completers achieved slightly higher results: BP goal achieved by 52.4% vs 53.7%, responders 80.5% vs 84.5%. This is not unexpected because LOCF analysis includes early results which have lower values (the drug has not reached its maximal effects).

Aml/Val caused decrease in BP which was greater in patients receiving higher dosage: with the exception of 10/160 mg (**Figure 2**). This could be because the 5/160 mg and 10/160 mg dosages were given to patients with higher grades of hypertension compared to patients receiving the 5/80 mg dosage.

For patients with ISH and the elderly, the decrease in BP followed the above pattern: the higher the baseline BP, the greater the decrease in BP and vice versa. It was shown very clearly in **Figure 4**, in ISH patients with very low DBP (<90 mmHg), Aml/Val produced very little decrease in DBP (mean -1.2 mmHg).

In the present study, the total number of patients with AEs, including SAEs was 11.4%, similar to the number found in the overall EXCITE study (11.2%).[20] The most frequent AE was also the same, it was edema in this subset study (3.7%) and in the overall study it was edema and peripheral edema (2.0% and 1.2%).[20] In the other real-world studies of Aml/Val, the total number of patients with AEs ranged from 1.4% to 8.8%1[8,19,21,22,28], and the most frequent AE was edema in 4 studies[18,19,21,22] and nausea in 1 study.[28]

There were 5 patients (1%) with SAEs in the present subset study which were considered unrelated to the study drug. Forty nine patients (0.6%) in the overall EXCITE study[20] had SAEs, the majority of these were considered unrelated to the study drug. In the other real-world studies with Aml/Val, between 0 (zero) to 8 patients[18,19,21,22,28] had SAEs, most of these SAEs were deemed not related to the study drug.

There were 4 deaths in the present study, and 12 deaths in the overall EXCITE study[20], none to 3 deaths in the other real-world studies of Aml/Val[18,19,21,22,28], but all of the deaths were considered not related to the study drug.

Among the 47 patients with edema at baseline, 28 patients had dihydropyridines as the prior antihypertensive treatment, and therefore they were likely the cause of the edema. The edema subsided in 25 of the 28 patients during treatment with Aml/Val, persisted in 2 patients

and 1 patient was unevaluable (patient had only baseline visit). Edema caused by DHPs (vasodilation) could be counter balanced by the venodilatory action of the angiotensin receptor blocker (valsartan).[29] The remaining 19 patients with edema at baseline did not receive previous CCBs, hence edema in these patients might be associated with the preexisting disease. The frequency of edema in the present study was 9.4% at baseline and 3.7% at study end. Compared to the other real-world studies of Aml/Val, in one study (N=2785)[18], edema at baseline was 13.7% and 10.1% at end of study, in the other study (N=9090)[19], edema at baseline was 10.4% and became 8.5% at study end, while in Pakistan subset study (N=471)[28] edema was 12.1% at baseline and 9.1% at study end. In the MAX-FORCE study (N=480)[21], edema at baseline was 3.5% and 0.4% at end of study.

Effectiveness, tolerability, and compliance were rated good or very good in around 90% of patients, similar to the overall EXCITE[20] and another real-life study[18], and higher compared to Pakistan subset study (only around 70%).[28]

The present study was a postmarketing observational study and hence there were several limitations. First, as an open study, it has no control group, and non-blinded measurement of outcomes were performed. Second, as an observational study, it has no standardized methods for data collection. These factors may cause observer bias, which limits the interpretation of the results. It is difficult to draw definitive conclusions from the results of the study.

However, an observational study from a real-life setting allows the inclusion of a wide variety of hypertensive patients, e.g. patients with different severities and different types of essential hypertension, patients with various concurrent diseases and concomitant medications. This heterogenous patient population with hypertension is more representative of the patient population encountered in routine clinical practice. It is encouraging that the BP reductions and the percentage of controlled BP in the present study are generally similar to the previous studies, whether in clinical trials[11-17] or in real-world setting.[18-22,28] Moreover, overall EXCITE study[20] includes mostly patients from the Middle-East and Asia, which have limited data on antihypertensive treatment.

Postmarketing (PM) results from this real-life setting reflect the real performance of the drug in daily clinical practice which is different from the highly restricted clinical trial setting. For medical practitioners, these PM results may be more applicable than the clinical trial results.

Another limitation is the subjective investigators' assessment on the effectiveness, tolerability, compliance and adherence to treatment. Nonetheless, these results indicated the levels of patient adherence in daily clinical practice.

CONCLUSION

Aml/Val SPC was effective and well tolerated for BP reductions in patients with various grades and various types of essential hypertension, not controlled by prior monotherapy, in a daily clinical setting in Indonesia.

CONFLICT OF INTEREST

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