Effectiveness and tolerability of fixed dose combination of amlodipine/valsartan in treatment of hypertension in the real-life setting among Egyptian patients

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Introduction: Many hypertension international guidelines recommend the use of fixed-dose combination of antihypertensive therapies as a first-line in high-risk hypertensive patients, in whom more rapid and pronounced blood pressure (BP) control is desired. The aim of this study was to evaluate the effectiveness, safety and tolerability of the single-pill combination of amlodipine/valsartan among Egyptian patients with arterial hypertension in a real-life setting.

Method: This prospective, open-label, multi-center, non-comparative post-marketing surveillance study enrolled adults with arterial hypertension (systolic BP >140 mmHg and/or diastolic BP >90 mmHg) treated with single-pill combination (SPC) of amlodipine/valsartan; 5/160 mg or 10/160 mg once daily dose. Patients were observed over a 3-months period with approximately monthly intervals between clinic visits. Primary objectives were comparison of systolic and diastolic blood pressure and heart rate at study start and after 12 weeks of therapy. Secondary objectives were evaluation of the blood pressure lowering effect in terms of response rates, evaluation of safety and tolerability of study medication.

Results: A total of 2489 patients were enrolled and 2357 completed the study. Mean age was 54 years and 85% of patients had received prior antihypertensive therapy. At study end, a significant mean BP reduction of −39.4/−21.7 mmHg (baseline: 171.5/103.4 mmHg; p < 0.001) was seen in the overall population. The corresponding mean BP reductions were: patients with diabetes; −41.1/−21.6 mmHg (baseline 173.2/103.5 mmHg; p = 0.00001), patients with history of heart failure; −45.2/−22.8 mmHg (baseline 175.9/104.6 mmHg; p = 0.00001), patients with history of coronary heart diseases; −43/22.7 mmHg (baseline: 175.8/105 mmHg; p = 0.00001). A small change in the heart rate was noticed (82 bpm at baseline and 78.4 bpm at the end of study; p < 0.001). 70.3% of patients had their blood pressure controlled (BP <140/90 mmHg). Subjective investigators assessment as “excellent to very good” for amlodipine/valsartan SPC was 97.3% for effectiveness and 96.8% for tolerability. The corresponding investigators and patients assessment for compliance was 96.6% and 93.3% respectively. Adverse events were reported in 4.4% of patients mainly due to edema in 3.6%. Amlodipine/valsartan SPC was generally well tolerated.

Conclusion: The Results of this study showed that Single-pill combination of amlodipine/valsartan effectively reduced BP among Egyptian hypertensive patients with high tolerability profile and provided evidence that most of hypertensive patients may benefit from this combination.

Introduction: High blood pressure is the most common cause of death estimated to affect at least 25% of all adults. The risk of cardiovascular disease doubles with every increase of 20/10 mmHg above a normal blood pressure. Antihypertensive medications not only lower blood pressure, but also reduce the risk of stroke or Cardiovascular diseases. Despite the availability of a wide range of antihypertensive medications, about 70% of hypertensive patients fail to achieve a blood pressure control target of less than 140/90 mmHg. Data from different national and regional surveys show that hypertension is common in developing countries, and the rates of awareness, treatment, and control are low. The increased prevalence in developing countries possibly caused by urbanization, ageing of population, changes of dietary habits, and social stress. Almost three-quarters of people with hypertension (639 million people) live in developing countries with limited health resources and where people have a very low awareness of hypertension and poor blood pressure control.
In Egypt, Patients aware of their disease accounts only for 37.5% of which 23.9% are treated and 8% only are controlled. The guidelines acknowledge that most patients with hypertension require 2 or more antihypertensive medications to achieve blood pressure control. Accordingly, initiation of therapy with 2 drugs is recommended in patients whose blood pressure is more than 20/10 mmHg above goal, either as separate agents or in a fixed-dose combination. One of the combinations recommended by the ESH/ESC guidelines is the combination of a calcium channel blocker with an angiotensin receptor blocker.

Fixed dose combination of Valsartan plus Amlodipine is an effective and well tolerated antihypertensive medication. Data showed that the two complementary mechanisms of action of calcium channel blocker and angiotensin receptor blocker helped more patients to reach their recommended blood pressure goals.

Furthermore, a recent study conducted on 8336 patients to evaluate the effectiveness and safety of amlodipine/valsartan single pill combination (SPC) showed that an optimal blood pressure (BP) reduction was achieved for all hypertension grades, including patients with isolated systolic hypertension. The treatment was well tolerated with few adverse events (AEs). Due to the fact of limited available data on Egyptian hypertensive patients, this study was planned to be conducted on large number of patients to show the results in real-life setting.

Methods: Study design Multicenter, observational, Post Marketing Surveillance (PMS) study. The total duration of treatment with SPC of amlopidine/valsartan 5/160 and 10/160 in this study was 12 weeks. In accordance with the definition of non-intervention studies, therapy was prescribed in terms of the marketing authorization. The assignment of patient to therapy was decided based on clinical evaluation and was separated from the decision to include the patient in the study. The dose of SPC of amlopidine/valsartan prescribed by the treating physician was recorded at the initial visit. Concomitant medications, including antihypertensive medications were allowed in the study. Patients were observed over a 3-months period. Patients could discontinue participation in the study for any reason. In the event of premature discontinuation, the investigators were requested to document the reason for discontinuation.

Patients: Males or females, >18 years of age, with hypertension (SBP/DBP >140/90 mmHg), for whom an antihypertensive therapy with the SPC of Valsartan 160 mg and Amlodipine 5 or 10 mg once daily is clinically recommended, were included in the study. All patients were asked to provide written informed consent before participating in the study. Women who were pregnant, intending to become pregnant or breastfeeding, patients with severe medical condition(s) that in the view of the investigator prohibits participation in the study e.g. severe renal or hepatic impairment and hypersensitivity to valsartan, amlodipine or any of the components in the formulation were excluded from the study. Independent ethical committee approval was obtained before the study initiation as per the local regulations.

Study procedures: At baseline, patients were assessed for demographic details, history, concomitant diseases, previous antihypertensive medications, blood pressure, and heart rate. Suitable dose of amlodipine/valsartan SPC was studied. The dose was adjusted during the follow up visits by the treating physician. Patients were monitored closely for change in SBP/DBP and heart rate during follow up visits for 12 weeks. Safety and tolerability assessments included the recording of adverse events (AEs) and serious adverse events (SAEs) throughout the study, irrespective to suspected relation to study medication. No additional diagnostic or monitoring procedures were performed. Primary end point was comparison of systolic and diastolic blood pressure and heart rate at study start and after 12 weeks of therapy with amlodipine/valsartan 5/160 mg or amlodipine/valsartan 10/160 mg. Secondary endpoint was evaluation of the blood pressure lowering effect in terms of response rates and evaluation of AEs and SAEs. Investigators entered the required patients’ data in the Case Report Form (CRF). It was entered anonymously into the study database, validated and analyzed.

Statistical analysis: A total of 2489 patients were enrolled and 2357 completed the study (Intent To Treat population). Analysis of results included descriptive statistics of the demographic data as well as efficacy and safety data. To determine statistical significance of efficacy and safety data, chi square test has been used to compare categorical results, while t-test has been used to compare two means and ANOVA for comparison of more than 2 means. Statistical significance limit was taken to be 0.05. Patients were analyzed as one group and were also divided into clinically relevant groups. In post-hoc analysis, patients were divided according to the prescribed dosage into 4 groups (up and down-titration were the decision of the treating physician); Group 1: Started amlodipine/valsartan 5/160 in V1 and maintained on amlodipine/valsartan 5/160 to V4 (33% of patients; n = 789), Group 2: Started amlodipine/valsartan 5/160 in V1 and increased to amlodipine/valsartan 10/160 in V2 or V3 (23% of patients; n = 535), Group 3: Started amlodipine/valsartan 10/160 at V1 and maintained on amlodipine/valsartan 10/160 to V4 (27% of patients; n = 630), Group 4: Started amlodipine/valsartan 10/160 at V1 and decreased to amlodipine/valsartan 5/160 to V4 (15% of patients; n = 344).

Results: Total of 2489 patients were enrolled in the study 2357 patients completed the four visits of the study and were evaluable for efficacy analysis. The baseline demographic details are shown in Table 1. 51.4% (n = 1212) of patients were on other concomitant medications. The leading concomitant diseases for which concomitant medications were indicated were: Diabetes (27.3%), Hypertension (13%), Hypercholesterolemia (11.8%), Ischemic Heart Diseases (11.7%),
Dyslipidemia (7.6%) and Hyperuricemia (6.1%). Eighty five percent of the patients were on antihypertensive treatment before the start of the study. Table 2 summarizes these antihypertensive medications.

**Antihypertensive efficacy:** The study results demonstrate that overall mean systolic blood pressure at baseline \((n = 2375)\) was 171.5 mmHg, it was reduced to 144.1 mmHg after 4 weeks, 135.8 mmHg after 8 weeks and 131.7 mmHg after 12 weeks with a very highly significant overall mean reduction of 39.8 mmHg; \(p < 0.0001\). Mean diastolic blood pressure at baseline was 103.4 mmHg, it was reduced to 88.8 mmHg after 4 weeks, 84.1 after 8 weeks and 82 mmHg after 12 weeks with a very highly significant overall mean reduction of 21.4 mmHg; \(p < 0.0001\) (see Fig. 1). In post-hoc analysis, significant reduction in BP after 12 weeks treatment with amlodipine/valsartan 5/160 and/or 10/160 in the four groups of patients. In Group 1 \((n = 789)\); mean reduction in SBP \(-34.6\) mmHg and DBP \(-19.1\) mmHg \((p < 0.0001)\), in Group 2 \((n = 535)\); mean reduction in SBP \(-36.3\) mmHg and DBP \(-19.9\) mmHg \((p < 0.0001)\), in Group 3 \((n = 630)\); mean reduction in SBP \(-47.1\) mmHg and DBP \(-24.3\) mmHg \((p < 0.0001)\), in Group 4 \((n = 344)\); mean reduction in SBP \(-44.9\) mmHg and DBP \(-23.7\) mmHg \((p < 0.0001)\) after 12 weeks of treatment Fig. 2.

**Blood pressure response rates:** BP control rates were also evaluated in our study Fig. 3. A total of 87.9% of patients had their SBP or DBP controlled \((<140\) or \(<90\) mmHg; respectively). Strict BP control \((BP <140/90\) mmHg) was achieved in 70.3% of patients. Percentage of patients reached SBP goal \((<140\) mmHg) was 73.9% and DBP goal \((<90\) mmHg) was 84.3%. Percentage of patients reached the BP goal \(<130/80\) mmHg was 31%.

**Heart rate:** There is a statistically significant decrease in heart rate from baseline to end of the study. Heart rate dropped from 82 bpm at baseline to 78.4 bpm after 12 weeks of treatment \((p<0.001)\).

**Blood pressure reduction by patients’ co morbidities:** When clinically relevant groups were analyzed, highly significant BP reduction was achieved Fig. 4. In patients with hypercholesterolemia (Group A); baseline SBP/DBP was 173.1/104.1 mmHg and reached 131.7/82.1 mmHg after 3 months \((-41.4/22\) mmHg; \(p = 0.00001)\). In patients with coronary heart diseases (Group B); baseline SBP/DBP was 175.8/105 mmHg and reached 132.8/82.3 mmHg after 3 months \((-43/22.7\) mmHg; \(p = 0.00001)\). In patients with Diabetes (Group C); baseline SBP/DBP was 173.2/103.5 mmHg and reached 132.1/81.9 mmHg after 3 months \((-41.1/21.6\) mmHg; \(p = 0.00001)\). In patients with hyperuricemia (Group D); baseline SBP/DBP was 173.3/104.7 mmHg and reached 131.1/82.1 mmHg after 3 months.
In patients with Heart Failure (Group E); baseline SBP/DBP was 175.9/104.6 mmHg and reached 130.7/81.8 mmHg after 3 months (\(p=0.00001\)).

In patients with respiratory diseases (Group F); baseline SBP/DBP was 174/103.7 mmHg and reached 134.1/82.8 mmHg after 3 months (\(p=0.00001\)).

Safety and tolerability: Combination amlodipine/valsartan was well tolerated in this study. Table 3. A total of 126 AEs were reported in 104 (4.4%) patients; 75 AEs were suspected by the treating physician to be related to study medication, 48 AEs were considered not related and, for 3 AEs, the physician’s evaluation was not provided. Of the reported adverse events, 77.6% were mild, 20.8% were moderate and 1.6% were severe.

Analysis of intensity of edema showed that at baseline, 77% had mild edema, 21% had moderate edema, and 2% had severe edema. After 12 weeks of treatment, 89% of edema cases were considered mild, 11% were moderate, and 1% were severe. SAEs were reported in 2 cases that died during the study. Deaths were due to complications resulting from duodenal ulcer and renal failure. Causes of death were assessed by the investigator as not related to study medication. Twenty-One patients had prematurely discontinued the Study medication. Reasons for premature discontinuation included lost follow up (9), adverse events (4), subjects no longer requiring the study drug (3), consent withdrawal (3) and death (2).

Table 3
Reported adverse events:

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>n, Patient (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>84 (3.6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (0.7%)</td>
</tr>
<tr>
<td>GIT disorder</td>
<td>8 (0.3%)</td>
</tr>
<tr>
<td>Elevated liver enzymes</td>
<td>5 (0.2%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>4 (0.2%)</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>4 (0.2%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3 (0.1%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (0%)</td>
</tr>
</tbody>
</table>

\(\text{Mean Change in BP (mmHg)} = -42.2/22.6\text{mmHg}; p = 0.00001\). In patients with Heart Failure (Group E); baseline SBP/DBP was 175.9/104.6 mmHg and reached 130.7/81.8 mmHg after 3 months (\(-45.2/22.8\text{mmHg}; p = 0.00001\)).

In patients with respiratory diseases (Group F); baseline SBP/DBP was 174/103.7 mmHg and reached 134.1/82.8 mmHg after 3 months (\(-39.9/20.9\text{mmHg}; p = 0.00001\)).

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Discussion: In this a post marketing observational study, designed to represent real-life setting, SPC of amlodipine/valsartan was shown to significantly reduce the BP. Analyses for patients with concomitant medical conditions (e.g.: hypercholesterolemia, Ischemic heart diseases, diabetes, and heart failure) demonstrated the antihypertensive efficacy of this combination among these populations.

The National Institute for Health and Clinical Excellence (NICE) Guideline Development Group stated that most of hypertensive patients require more than one drug to reach the BP goal. For hypertensive patients whose blood pressure is not controlled by A (ACEi or
ARBS) in young adults (≤ 55 years) and C (CCBs) or D (Diuretics) in older patients (>55 years) which is step 1 treatment. If failed, step 2 should be considered as a combination of A + C or A + D.6

Combination of ARB/CCB provides enhanced blood pressure lowering efficacy compared with the effect of ARBs or CCBs as monotherapies and may promote a counter-regulatory response. Activation of sympathetic nervous system by CCB induced vasodilatation is diminished by blockade of RAAS with ARB. The antihypertensive effect of the ARB/CCB combination may not be only additive but also synergetic.7

The results of our study supported the results of previously conducted amlodipine/valsartan randomized controlled clinical studies. Dose dependent BP lowering by amlodipine/valsartan combination was demonstrated by Philipp et al.8 and further analysis performed by Smith et al.9 confirmed that the degree of BP lowering corresponded to the initial hypertension stage. Poldermans et al study provided evidence that in patients with mean BP 180/110 mmHg amlodipine/valsartan combination provided a SBP reduction of ≈ 43.0 mmHg and it was numerically greater than that provided by lisinopril/hydrochlorothiazide combination in this subgroup of patients (−31.2 mmHg).10

In our study, a reduction of the SBP of −39.8 mmHg and −21.4 mmHg in DBP confirms that amlodipine/valsartan combination is effective in lowering BP. This is consistent with results of large post marketing study included 2785 hypertension patients demonstrated that amlodipine/valsartan combination significantly reduces BP in patients with arterial hypertension. The BP lowering effect was dose dependent and also corresponded to the baseline level of BP elevation.11 In this observational study, single-pill combination amlodipine/valsartan was shown to significantly reduce BP in a manner that was dose dependent and corresponded to the severity of baseline BP confirming the previous evidences.

Another observational study has reported the same efficacy profile with overall mean BP reduction after a 12-week course of SPC of amlodipine/valsartan as −36.3/−18.9 mmHg (mean BP of 165.0/99.3 mmHg at week 1 vs. 128.7/80.4 mmHg at week 12).12

Another interesting finding in our study is that there was a significant decrease in heart rate from baseline to end of the study, providing evidence that there was no unfavorable effect of amlodipine in combination with valsartan on heart rate as one could expect.

Peripheral edema is a well-known dose-dependent and dose-limiting side effect of treatment with CCBs, recognized as a consequence of imbalances involving hydrostatic and oncotic pressure gradients and vascular permeability.13 A recent meta-analysis of CCB-based antihypertensive therapy found that the incidence of, and treatment withdrawal rate for, this toxicity increased with the duration of therapy, with 24% of patients reported peripheral edema and 5% of patients with peripheral edema-related discontinuation after 6 months.14 Administering a CCB in conjunction with a Renin Angiotensin Aldosterone System (RAAS) blocker is among the proposed means for mitigating both the incidence and severity of CCB-related peripheral edema15,16 demonstrating a 38% lower incidence of peripheral edema versus CCB monotherapy (relative risk, 0.62; P < 0.00001) as well as a 62% reduction in the risk of peripheral edema-related withdrawal (relative risk, 0.38; P < 0.01). In a real life setting study, a 8.5% incidence of peripheral edema at study end was reported as well.17

In the current study, Incidence of edema had not increased, on the other hand; the severity of edema was decreased at the end of the study. The reduction in severity of peripheral edema over time reflects the complementary mechanism of action of the CCB and ARB classes.

In the current study also, clinically relevant groups were analyzed in a post-hoc analysis, a highly significant BP reduction with amlodipine/valsartan single pill combination was achieved in patients with hypercholesterolemia with −41.4/22 mmHg reduction from baseline, patients with coronary heart diseases −43/22.7 mmHg from baseline, in patients with diabetes −41.1/21.6 mmHg reduction from baseline and in patients with heart failure −45.2/22.8 mmHg reduction from baseline with good safety and tolerability profile.

Compliance is defined by the World Health Organization (WHO) as “the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”.18 In relation to the management of hypertension, poor patient compliance is one of the most common causes of patient’s failure to reach BP control, on the other hand; There was a positive association between BP control and compliance, about 75% of compliant patients achieve BP <140/90 mmHg, compared with only 10% of non-compliant patients.19 In the Canadian Hypertension Education Program (CHEP) 2013, adherence and non-adherence to healthy lifestyle and pharmacotherapy is an important cause of poor blood pressure control. Patient adherence to lifestyle modifications and pharmacotherapy should be assessed on each visit and interventions to improve adherence should be a part of routine clinical practice. Strategies to improve patient adherence are: (i) Simplifying medication regimen to one-daily dosing; (ii) Replacing multiple pill antihypertensive combinations with single pill combinations.20 Costa et al., mentioned that, when considering together monotherapy and fixed-dose combinations, ARBs showed the highest persistence rate among all antihypertensive medications; among ARBs, valsartan has the lowest risk of non-persistence.21 These findings and recommendations are matched with and may explain high patients’ satisfaction results with valsartan/amlodipine fixed dose combination in our study.

Also, As regards investigators assessment of amlodipine/valsartan SPC, 78.1% assessed it as excellent regarding efficacy 75.6% regarding tolerability. 70.7% of patients rated tolerability to Amlodipine/valsartan combination as Excellent.

Limitations: This study was non-randomized, uncontrolled, and observational in nature. Limitations of observational studies in general include the potential for observational bias due to lack of blinding and the absence of standardized data collection. The real-life setting of the current study does not allow the authors to make definitive conclusions concerning comparative efficacy and safety of the studied combination. On the other hand, the observational design of this study made possible the acquisition of a large amount of data in a broad population of hypertensive patients with a variety of clinical conditions and comorbid diseases, which makes the results more relevant to real clinical practice.

Conclusion: In a large cohort of uncontrolled hypertensive patients, SPC of amlodipine/valsartan provided effective blood pressure reduction and control with good tolerability. This data provides beneficial evidence of this combination in Egyptian hypertensive patients.

Conflict of interest: Nashwa Nashaat; Medical Manager at Novartis Pharma S.A.E helped in writing this paper with the authors.

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