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Blood Pressure Control and Quality of Life in Hypertensive Patients Treated with Amlodipine/Valsartan Fixed Dose Combination – IMPROVE Study Results

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Abstract

Aim: To evaluate the efficacy in controlling blood pressure (BP) values and the influence on the quality of life (QOL) of amlodipine-valsartan fixed combination treatment in hypertensive patients. **Method:** An open-label, multicentre (560 centres), prospective (4 study visits, 12 months) observational, non-interventional, enrolling patients on amlodipine-valsartan fixed dose combination. BP control was defined by SBP <140 mmHg and DBP <90 mmHg. QOL was evaluated using SF-12 questionnaire. **Results:** Study sample: 3293 hypertensives, mean age 62.82±10.91 years, 58.4% females, mean BP: 169.71±17.25 / 95.48±11.29 mmHg. There was a continuous descending trend in BP values (SBP - 169.82 mmHg vs. 142.93 mmHg vs. 137.08 mmHg vs. 134.61 mmHg; DBP - 95.56 mmHg vs. 82.64 mmHg vs. 79.69 mmHg vs. 78.31 mmHg) and an increase in the proportion of controlled BP values (from 2% up to 60,1%). Proportion of patients with QOL above average increased throughout the study (PCS: 46% vs. 52.5% vs. 55.8% vs. 58.6%; MCS - 46% vs. 58.7% vs. 61.4% vs. 62.3%). There was a significant association between BP control and QOL, independent of age, sex and base-line BP values. **Conclusions:** Through optimal BP control, amlodipine-valsartan fixed dose combination proved to have a significant effect on QOL of treated hypertensive patients and leading to a high treatment persistence rate.

Keywords: hypertension, fixed dose combination, amlodipine, valsartan, quality of life, blood pressure control.

Abstract

Obiectiv: Evaluarea eficacității în controlul tensiunii arteriale (TA) şi a influenței asupra calității vieții (QOL) a combinatiei fixe amlodipină-valsartan la pacienții hipertensivi. **Metoda:** Studiu multicentric (560 centre), prospectiv (studiu 4 vizite, 12 luni) observational, non-intervențional, ce a inrolat hipertensivi aflati in tratament cu combinația fixă amlodipină-valsartan . Controlul TA a fost definit prin TAS <140 mmHg şi TAD <90 mmHg. QOL a fost evaluată folosind chestionarul SF-12. **Rezultate:** Lotul de studiu: 3293 hipertensivi, vârsta medie 62.82±10.91 ani, 58,4% femei, media valorilor TA: 169.71±17.25 / 95.48±11.29 mmHg. Pe parcursul studiului a existat o tendință descrescătoare continuă a valorilor TA (TAS - 169.82 mmHg vs 142.93 mmHg vs 137.08 mmHg vs 134.61 mmHg; TAD - 95.56 mmHg vs 82.64 mmHg vs 79.69 mmHg vs 78.31 mmHg) şi o creştere a continuă a cazurilor cu TA controlată (de la 2% până la 60,1%). Proporția de pacienți cu QOL peste medie a crescut pe parcursul studiului (PCS-uri: 46% față de 52,5% vs. 55.8% vs. 58.6%; MCS - 46% vs. 58.7% vs. 61.4% vs. 62.3%). Studiul a evidențiat o asociere semnificativă

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între controlul TA şi QOL, independentă de vârstă, sex şi valorile TA de la înrolare. **Concluzii:** Printr-un control optim al TA, combinația fixa amlodipina-valsartan s-a dovedit a avea un efect semnificativ asupra QOL pacienților hipertensivi tratati conducând la o rată mare de aderență la tratament.

Cuvinte cheie: hipertensiune, combinație fixă, amlodipine, valsartan, calitatea vieții, control

INTRODUCTION

High blood pressure is the world's most common cause of death, estimated to affect at 4 out of 10 Romanian adults[1-3].

Despite the availability of a wide range of antihypertensive drugs, about 70% of treatment hypertensive patients fail to achieve the blood pressure target of less than 140/90 mmHg recommended by the current guidelines[4,5]. In Romania, less than one quarter of treated hypertensive adults have a controlled blood pressure (less than 140/90 mmHg)[1-3,6,7].

Since 2007 ESH-ESC Guidelines for the Management of Hypertension[8], we acknowledge that the ability of any antihypertensive agent used alone to achieve target BP values (<140/90 mmHg) does not exceed 20-30% of the overall hypertensive population except in subjects with grade 1 hypertension. Furthermore, the combination treatment should be considered as first choice particularly when initial BP is in the grade 2 or 3 range or total cardiovascular risk is high or very high (e.g. patients with diabetes mellitus, metabolic syndrome, subclinical organ damage or established cardiovascular or renal disease)[4].

Low adherence to hypertension treatment is the most important cause of uncontrolled blood pressure and there are several factors: therapy-related factors, socio-economic related factors and patient related factors. This last factor involve: inadequate knowledge and skill in managing the disease symptoms and treatment, lack of awareness of benefits of the treatment, disturbed perception of health risk related to the disease. Behavioural and motivational intervention, as well as medical education provided to the hypertensive patient may improve adherence and consequently quality of life[9].

Antihypertensive drugs of different classes can be combined if they have different and complementary mechanisms of action, if there is evidence that the antihypertensive effect of the combination is greater than that of either combination component and if the combination may have a favourable tolerance profile, the complementary mechanisms of action of the components minimizing their individual side effects[4].

One of the combinations recommended by current ESH-ESC guideline is the combination of a calcium channel blocker (CCB) with an angiotensin receptor blocker (ARB). Therapy with an ARB and a CCB has the potential to provide prompt reductions in blood pressure that would be expected to reduce the risk of cardiovascular morbidity and mortality. In addition, ARBs and CCBs have both been associated with protective benefits beyond BP control[10].

Amlodipine-valsartan is a fixed combination antihypertensive agent that lowers BP and attenuates compound-specific adverse events, such as amlodipine-related peripheral oedema. Currently available data show that amlodipine-valsartan is a well-tolerated agent that gets patients with severe hypertension to their BP goal[11].

Quality of life in hypertensive patients is influenced by treatment efficacy which can be severely compromised by poor adherence to long-term therapies.

Symptoms, whether disease or treatment induced, may impair the health-related quality of life (QOL) of patients. QOL refers to the physical, emotional and social impact of disease and treatments, and is distinct from the physiological measures of disease. QOL measures may capture the impact of the disease and its treatment from a patient perspective more than conventional clinical symptom measures do. To measure QOL, a questionnaire with 36 health related QOL (SF-36) items has been developed and validated within the context of hypertension[12]. Moreover, a shorter form of the SF-36 has been developed with 12 items (SF-12), which has been shown to be a valid alternative to the SF-36 for clinical practice or research purposes when studying hypertensive individuals and their treatment. It covers eight domains, including physical functioning, role-physical, bodily pain, general health, vitality, social functioning and role emotional and mental health[13].

OBJECTIVES

The aim of this study is to evaluate the efficacy in controlling blood pressure values and the influence on the quality of life of amlodipine-valsartan fixed dose combination treatment in hypertensive patients.

METHODS

This is an open-label, multicentre, prospective, observational, non-interventional, post-marketing surveillance (PMS) study implemented in 560 centres with the goal of enrolling up to 5678 patients on amlodipine-valsartan fixed dose combination, comprising 4 study visits: enrolment (V0), 4 months' follow-up (V1), 8 months' follow-up (V2) and 12 months' follow-up (V3).

Fixed dose combinations (5/80 mg, 5/160 mg, 10/160 mg) were prescribed according to patient's needs and at the discretion of the physician. Up-titration was adapted to each patient according to necessary and tolerated individual doses. If considered necessary by the physician, additional antihypertensive was permitted in each individual treatment schemes for better BP control. All other concomitant antihypertensive and any concomitant medication administered to each patient, were observed and registered, in order to have better evaluation of the patient adherence to multiple regimes treatment.

Office systolic and diastolic blood pressure values, measured according current ESH-ESC guidelines, were recorded at each study visit in order to evaluate efficacy of amlodipine-valsartan fixed dose combination in controlling blood pressure value at the end of the study.

Blood pressure control was defined by SBP values less than 140 mmHg and DBP values less than 90 mmHg.

Quality of life for hypertensive patients was evaluated using SF-12 questionnaire and was assessed in relation to fixed dose combination treatment. Due to SF-12 score dependency on age, SF-12 score analysis was performed by age categories (18-34 years, 35-44 years, 45-54 years, 55-64 years, 65-74 years and ≥75 years), each individual SF-12 score being analysed in reference to the SF-12 score recoded in each specific age group. Score difference between individual SF-12 score and mean SF-12 score of the age group was computed for each enrolled patients. Those patients with a negative score difference was considered as having below average quality of life, while those patients with a positive score difference were considered as having above average quality of life.

Safety assessments consisted in monitoring and recording all adverse events and serious adverse events.

Statistical analysis

An intention-to-treat analysis was performed using IBM SPSS Statistics 20.0 software at a significance level of $p < 0.05$.

Chi-square, Mann-Whitney U, Friedman and Wilcoxon tests were used to validate the statistical significance between proportion a means respectively.

Bivariate correlation analysis (Spearman correlation coefficient calculation) was used to validate the association between QOL score and fixed dose combination treatment BP control.

RESULTS AND DISCUSSION

General characteristics of the study sample

A total number of 3293 hypertensive patients were included in the study according to the inclusion and exclusion criteria.

Mean age of the study sample was 62.82±10.91 years (range: 27-94 years) with a female preponderance (1909 subjects, 58.4%). Mean BP values were 169.71±17.25 / 95.48±11.29 mmHg and mean HR was 77.33±9.16 bpm.

The majority of hypertensive subjects were treated (3006 subjects, 91.3%) in their majority with 2 antihypertensive drugs (1230 subjects, 40.92%).

Among hypertensive patients receiving monotherapy at study inclusion, angiotensin converting enzyme inhibitors (ACEIs) were the most frequently recorded drugs (520 subjects, 56.7%). Monotherapy with calcium channel blockers (CCBs) were recorded in 53 cases (10.2%) out of which amlodipine was recorded in 6.5% of cases. Monotherapy with angiotensin receptor blockers (ARBs) was recorded in 48 cases (9.2%) out of which valsartan was recorded in only 1.9% of cases.

The most frequently recorded double therapy at study inclusion was ACEIs + thiazide (1229 cases, 37%), while CCB + ARB was recorded in only 32 cases representing 2.6% from the hypertensive patients receiving double therapy.

Beta-blocker + ACEIs+ thiazide was the most frequently recorded triple therapy at study inclusion (887 cases, 32.7%), while triple therapy including ARB+CCB was recorded in only 98 cases (11%).

Amlodipine-Valsartan fixed combination treatment

The main reason for initiation of amlodipine-valsartan fixed dose treatment was the lack of BP control under previous antihypertensive treatment (2599 cases, 78.9%).

The most frequently recommended amlodipine-valsartan fixed combination dose at first study visit was 5/160 mg [5/80 mg – 1081 cases, 33.2% vs. 5/160 mg – 1214 cases, 37.3% vs. 10/160 mg – 960 cases, 29.5%;

p <0,0001]. Subsequently, amlodipine/valsartan 5/160 mg remained the most frequently used dosage throughout the study. Also, the proportion of hypertensive patients treated with amlodipine-valsartan 5/160 mg was statistically similar through the study (Figure 1).

At study end, the proportion of hypertensive patients treated with amlodipine-valsartan 10/160 mg significantly increased from 29.5% at the first study visit up to 35.9%. The first significant increased in the proportion of hypertensive patients treated with this dosage was recorded at the second study visit (4 months after fixed dose treatment initiation) [V0:29.5% vs. V1: 34.6%; p<0,0001]. Afterwards, the proportion of the hypertensive patients treated with amlodipine-valsartan 10/160 mg remained statistical similar [V1:34.6% vs. V2: 35.8%; p=0.078; V2:35.8% vs. V3: 35.9%; p=0.444] (Figure 1).

Blood pressure values evolution across the study

Systolic and diastolic blood pressure values' evolution across the four study visits are detailed in Table 1.

After 12 months of treatment with amlodipine-valsartan fixed dose combination, systolic blood pressure (SBP) values significantly decreased, on average with 35,21mmHg than SBP values recorded at study beginning, with 8.32 mmHg than SBP values recorded after 4 months of treatment and with 2.47 mmHg than SBP values recorded after 8 months of treatment respectively. There was a continuous descending trend in SBP values across the study [V1>V0; z = -46.75; p <0.0001; V2>V1; z = -24,84; p <0.0001; V3>V2; z = -14.45; p <0.0001] (Figure 2).

Similarly, at the final study visit, diastolic blood pressure (DBP) values significantly decreased, on average with 17.25 mmHg than DBP values recorded at study beginning, with 4.33 mmHg than DBP values recorded after 4 months of treatment and with 1.38 mmHg than SBP values recorded after 8 months of treatment respectively. There was a continuous descending trend in DBP values across the study also [V1<V0; z = -42.94; p<0.0001; V2<V1; z = -18.19; p<0.0001; V3<V2; z = -9.74; p<0.0001] (Figure 3).

Comparing with the study beginning, when only 2% (67 cases) of patients had controlled BP values, across the study there was a continuous and significant increase in the proportion patients with controlled BP values, up to 60,1% (1871 cases) after 12 month of treatment with amlodipine/valsartan fixed dose combination (Figure 4).

SF-12 scores' evolution across the study

Physical (PCS) and mental (MCS) component scores across the four study visits by age groups are detailed in Table 2.

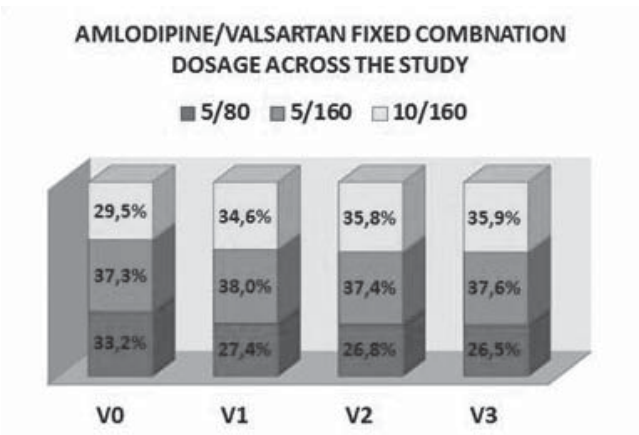

Figure 1.

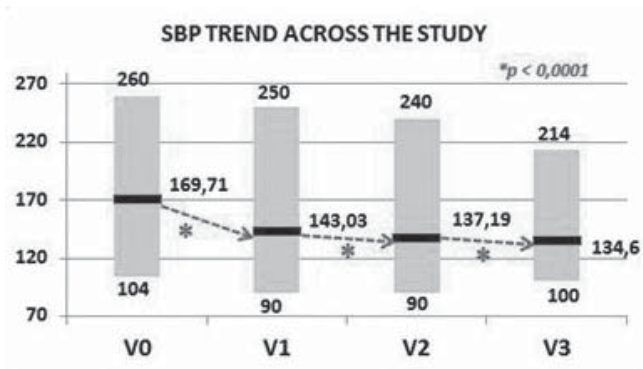

Figure 2.

Table 1. Blood pressure values' evolution across the study

	V0	V1	V2	V3	p*
SBP (mmHg)	169.71±17.25 (104-260)	143.03±14.48 (90-250)	137.19±13.15 (90-240)	134.60±12.84 (100-214)	<0.0001
DBP (mmHg)	95.48±11.29 (48-220)	82.67±9.33 (50-125)	79.74±8.77 (40-185)	78.31±8.54 (50-140)	<0.0001

Values are presented as mean ± s.d. (range) for continuous data; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; *Friedman's test

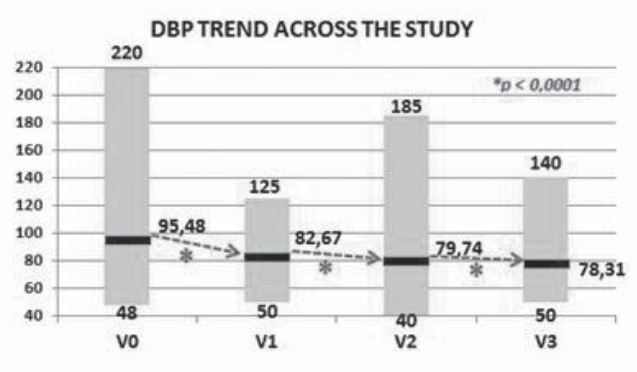

Figure 3.

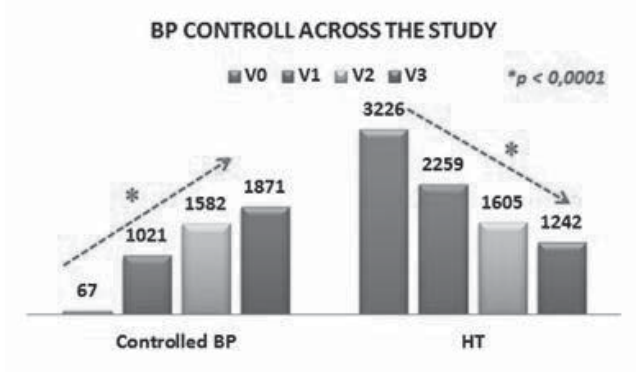

Figure 4.

There has been a statistical significant continuing increase in both PCS and MCS across the study in all age groups except for the 18-34 years' group, where after a significant increase of both PCS and MCS at V1 comparing with V0, these values remained at similar values throughout the rest of the study (Figure 5A and B).

In all age groups, the highest increase in both PCS and MCS was recorded after 4 months of treatment with amlodipine-valsartan fixed dose combination (V1).

Quality of life assessment across the study

Throughout the study, the proportion of hypertensive patients with QOL above average regarding the physical component, significantly increased from 46% at study entry up to 58,6% at 12 months after amlodipine-valsartan fixed dose treatment initiation [V0: 46% vs. V1: 52.5%; p <0.0001; V1: 52.5%; vs. V2: 55.8%; p <0.0001; V2: 55.8% vs. V3: 58.6%; p <0.0001] (Figure 6).

Table 2. SF-12 scores' evolution across the study

SF-12 PCS	**V0**	**V1**	**V2**	**V3**	**p***
18-34 years	45.76±8.53 (29.4-55.3)	51.8±6.06 (37.7-56.6)	52.4±6.92 (37-57.2)	53.02±5.81 (39.2-56.6)	<0.0001
35-44 years	42.94±8.95 (19 – 61.4)	49.05±7.24 (25.1-62.4)	50.91±6.45 (29.6-61.3)	52.17±5.61 (28.1-61.9)	<0.0001
45-54 years	41.39±9.14 (19.4-60.1)	47.35±7.81 (23.1-62.16)	49.33±7.14 (23.7-59.9)	50.97±6.34 (24.6-62.8)	<0.0001
55-64 years	39.27±9.36 (16.9-61.2)	44.46±8.23 (18.6-61.36)	47.11±7.93 (22.3-61.5)	48.67±7.39 (21.4-61.5)	<0.0001
65-74 years	36.17±8.92 (16.5-58.1)	41.87±8.37 (20.7-61.9)	44.45±8.66 (20.4-61.4)	46.25±8.52 (22.9-61.1)	<0.0001
≥ 75 years	33.87±8.54 (15.9-55.5)	37.98±8.44 (16.9-59.6)	39.86±8.85 (21.4-59.1)	41.96±8.99 (21.4-58.5)	<0.0001
SF-12 MCS	**V0**	**V1**	**V2**	**V3**	**p***
18-34 years	47.63±13.75 (14.1-62.2)	52.57±10.73 (26.7-60.8)	54.85±8.98 (31-60.8)	53.96±9.22 (32-60.8)	<0.0001
35-44 years	48.63±10.91 (19.3 – 67.1)	52.61±9.15 (23.3-63.2)	54.43±7.58 (18.8-61.7)	56±5.78 (33.6-61.6)	<0.0001
45-54 years	45.52±11.37 (16.4-64.1)	52.41±8.40 (23.6-68.1)	54.02±7.21 (17.6-64.7)	55.01±6.72 (20.5-68.9)	<0.0001
55-64 years	45.16±11.81 (15.3-68.1)	50.37±9.65 (15.3-66.3)	52.64±8.69 (17.4-68)	53.57±8.29 (19.6-68)	<0.0001
65-74 years	42.78±11.96 (13.4-67.9)	47.99±10.26 (15.3-68.3)	50.36±9.41 (7.5-65.6)	51.88±8.98 (19.3- 66.9)	<0.0001
≥ 75 years	41.03±11.62 (17.1-63.6.5)	45.47±10.39 (19.3-66.9)	47.46±9.91 (20.2-68.1)	48.62±9.57 (20.5-66.5)	<0.0001

Values are presented as mean ± s.d. (range) for continuous data; SF-12: short form 12; PCS: physical component score; MCS: metal component score; *Friedman's test

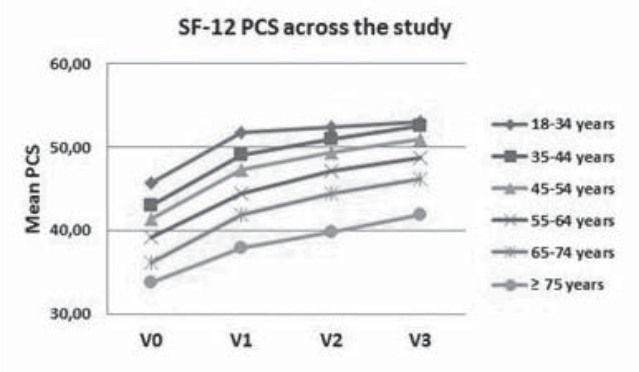

Figure 5A.

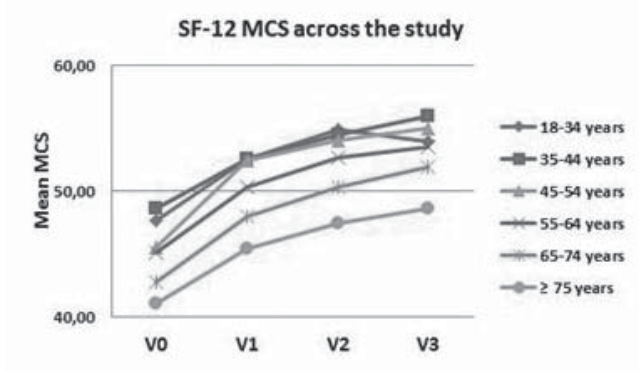

Figure 5B.

Also, at every study visit, the proportion of hypertensive patients with QOL above average regarding physical component, was significantly higher among those with controlled BP values (Table 3).

Likewise, the proportion of hypertensive patients with QOL above average regarding the mental component, significantly increased from 46% at study entry up to 62.3% at 12 months after amlodipine-valsartan fixed dose treatment initiation [V0: 46% vs. V1: 58.7%; p<0.0001; V1: 58.7%; vs. V2: 61.4%; p = 0,001; V2: 61.4%vs. V3: 62.3%; p = 0.149].

It is worth mentioning that the proportion of hypertensive patients with QOL above average, regarding the mental component, recorded at 12 months (V3) is similar to the proportion recorded at 8 months (V2). Also, at every study visit, the proportion of hypertensive patients with QOL above average regarding mental component, was significantly higher among those with controlled BP values (Table 3).

Bivariate correlation analysis revealed a significant direct association between BP control after initiation of amlodipine-valsartan fixed dose treatment and the

Table 3. SF-12 scores' evolution across the study

QOL- PCS	**Controlled BP**	**Uncontrolled BP**	**p***
V0 (initiation)			
• Above average	46 (69.7)	1450 (45.5)	<0.0001
• Below average	20 (30.3)	1735 (54.5)	
V1 (4 months)			
• Above average	363 (63)	1056 (47.8)	<0.0001
• Below average	374 (37)	1155 (52.2)	
V2 (8 months)			
• Above average	1034 (66.6)	707 (45.1)	<0.0001
• Below average	519 (33.4)	861 (54.9)	
V3 (12 months)			
• Above average	1219 (67.2)	555 (45.6)	<0.0001
• Below average	596 (32.8)	661 (54.4)	
QOL - MCS	**Controlled BP**	**Uncontrolled BP**	**p***
V0 (initiation)			
• Above average	46 (69.7)	1450 (45.5)	<0.0001
• Below average	20 (30.3)	1735 (54.5)	
V1 (4 months)			
• Above average	655 (64.9)	1239 (56)	<0.0001
• Below average	355 (35.1)	975 (44)	
V2 (8 months)			
• Above average	1045 (67.3)	873 (55.7)	<0.0001
• Below average	508 (32.7)	695 (44.3)	
V3 (12 months)			
• Above average	1230 (67.8)	659 (54.2)	<0.0001
• Below average	584 (32.2)	557 (45.8)	

Values are presented as absolute number (percent) for categorial data; SF-12: short form 12; PCS: physical component score; MCS: metal component score; BP. blood pressure; V0: first study visit; V1: second study visit (at 4 months after treatment initiation); V2: third study visit (at 8 months after treatment initiation); V3: forth study visit (at 12 months after treatment initiation);**chi* square test.

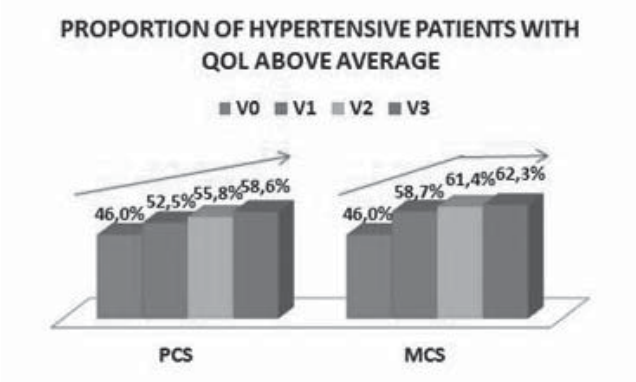

Figure 6.

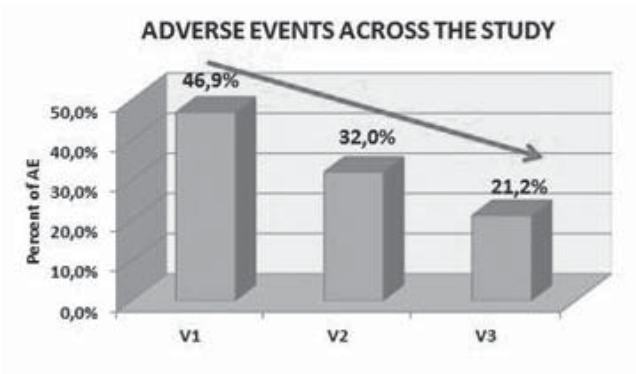

Figure 7A.

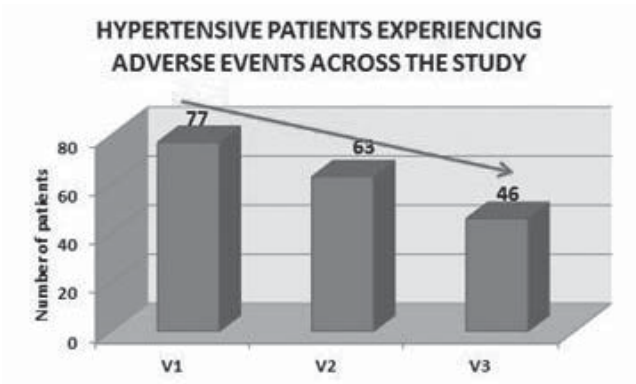

Figure 7B.

quality of life of treated hypertensive patients, the presence of controlled BP values being more frequently associated with a QOL above average, association that remained statistically significant after adjustments for age, sex and base-line BP values:

- Physical component score - V0: r_s = 0.068; p<0.0001; V1: r_s = 0.141; p<0.0001; V2: r_s = 0.216; p< 0.0001; V3: r_s 0.214; p<0.0001
- Mental component score - V0: r_s = 0.068; p<0.0001; V1: r_s = 0.084; p<0.0001; V2: r_s = 0.119 p<0.0001; V3: r_s 0.138; p<0.0001

The value of the correlation coefficients between BP control and QOL are higher for PCS compared with those for MCS implying that treatment with amlodipine-valsartan fixed dose combination has a more pronounced impact on physical component of QOL rather than on the mental one.

Amlodipine-valsartan fixed dose combination safety and persistence rate

A total number of 161 patients experienced a total number of 241 adverse events were recorded, out of which 9 were serious adverse events (deaths) and 232 minor adverse events recorded in 152 patients. The overall serious adverse event rate was 0.0027 per patient and overall minor adverse events rate was 0.0695 per patient. The most frequent minor AE was oedema – 54 cases, 24% from all AE.

Throughout the study, there was a continuing descending trend of both the total number of AE and the total number of patients experiencing AE (Figure 7A and B).

At the end of follow-up, 3080 patients remained in treatment with amlodipine/valsartan fixed dose combination, accounting for a treatment persistence rate of 93.5%.

CONCLUSIONS

Amlodipine-valsartan fixed dose combination proved to be efficient and safe in controlling BP values in hypertensive patients after 12 months of treatment. More, this treatment proved to be effective starting within the first 4 months of treatment.

Through optimal BP control, this fixed dose combination proved to have a significant effect on the quality of life of treated hypertensive patients increasing the QOL above the average level expected for age and leading to a high treatment persistence rate.

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