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Meta-analysis of three observational studies of amlodipine/valsartan in hypertensive patients with additional risk factors

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Abstract

Objectives. In this study, the effectiveness of amlodipine/valsartan single-pill combination was assessed in hypertensive patients with diabetes, metabolic risk or overweight. *Methods.* Data from 12,265 patients treated with amlodipine/valsartan from three studies were analyzed in a meta-analysis. These studies focused on (i) non-diabetic hypertensive patients suffering from abdominal obesity; (ii) hypertensive patients with at least one metabolic risk factor; and (iii) hypertensive patients with type 2 diabetes mellitus. The observation periods were 16 weeks for the first two and 24 weeks for the latter cohort. *Results*. At start of observation, the mean blood pressure was 162.3 mmHg (systolic) and 93.5 mmHg (diastolic). A total of 7.4% of patients were aged ≥ 80 years. At end of the observation, a normalized blood pressure was present in 38.8% of patients. No appreciable differences in blood pressure reduction were evident between the study groups. In both age subgroups (< 80 years and ≥ 80 years) blood pressure reduction was comparable. Tolerability was assessed by treating physicians as "very good" (69.3%) and "good" (27.3%). *Conclusions*. In daily practice, treatment of hypertensive patients with additional risk factors with amlodipine/valsartan single-pill combinations is well tolerated and associated with effective reduction of blood pressure.

Keywords: *Amlodipine, diabetes mellitus, hypertension, meta-analysis, risk factors, valsartan*

Introduction

In everyday practice, the treatment of patients with hypertension is challenging since patients frequently suffer from co-morbid conditions like diabetes, chronic kidney disease and specific metabolic risk factors (1,2).

Physical inactivity, unhealthy diet and excess weight increase the risk of hypertension and cardiovascular disease (1,3,4). It might lead to hypertension and cardiovascular disease, e.g. by activating the renin–angiotensin–aldosterone system. Based on population studies, risk estimates indicate that at least two-thirds of the prevalence of hypertension can be directly attributed to obesity (5). Physical inactivity, unhealthy diet and overweight become particularly important in the elderly.

Hypertension in the elderly has gained considerable attention. The prevalence of hypertension in people above 60 years of age approaches 60–70% (6). In this age group, a much higher risk of cardiovascular morbidity and mortality is observed compared with middle-aged patients with hypertension. Multiple mechanisms, such as stiffening of large arteries, endothelial dysfunction, autonomic dysregulation as well as renal dysfunction, contribute to the higher prevalence of hypertension in the elderly and to increased cardiovascular morbidity and mortality (7–11). The benefits of treatment in this age group have been demonstrated in various studies (8). The results of the HYVET trial (12) indicate that antihypertensive treatment significantly lowers the risk of death from stroke and death from any

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cause as well, in patients aged ≥ 80 years. The finding for stroke is in accordance with the results from the HYVET pilot study (13) as well as from a meta-analysis of publications dealing with antihypertensive therapy in very old patients (14). Some trials (15,16) were also done in elderly patients with isolated systolic hypertension.

The outcome of monotherapy is often unsatisfactory even with up-titration of the prescribed drug. Monotherapy is advised as an initial treatment when blood pressure (BP) elevation is mild with a low or moderate total cardiovascular risk. By contrast, a combination of two drugs at low doses should be preferred as the first step treatment when initial BP is in grade 2 or 3 and/or total cardiovascular risk is high or very high (17). More than two-thirds of patients will need two or more agents from different drug classes to achieve the recommended BP of < 140/90 mmHg (< 130/80 mmHg for diabetic and hypertensive high-risk patients). Compliance is enhanced by combination therapy in a single tablet as a result of a simplification of treatment.

One recommended synergistic drug combination is that of a calcium channel blocker and of an angiotensin II receptor blocker. The efficacy and safety of one such possible combination, the combination of amlodipine/valsartan, has been proved in clinical studies (18,19). Moreover, there is evidence that a combination with valsartan leads to a reduction in the incidence of peripheral edema (20), which is a known adverse effect associate with use of amlodipine, especially at higher doses.

In Germany, the prevalence of uncontrolled or poorly controlled hypertension is approximately 80% (21). Earlier studies have also shown that the prevalence of hypertension in Germany was rather high compared with the USA and other European countries (22,23). Herein, large-scale data pertaining to demographic characteristics and outcomes of specific therapies are sparse.

To obtain data from a real life setting in a large patient population in Germany, with a considerable number of very elderly patients and patients with a high body mass index (BMI), we conducted a meta-analysis of the data from three prospective observational studies. Data pertaining to the group of very elderly patients in Germany are limited. For instance, the HYVET study (12), aiming to find whether the treatment of hypertensive patients above 79 years of age is beneficial, only included 86 patients from Western Europe. By contrast, in the present study 905 participants from Germany were aged ≥ 80 years. The observational studies being reported here had evaluated the therapeutic effectiveness and safety of the single-tablet combination of amlodipine and valsartan in hypertensive patients with the following co-morbid conditions: being overweight, metabolic risk factors or type 2 diabetes mellitus. We also investigated certain subgroups of this patient population, especially the very elderly and those with different BMI classes.

Methods

Study cohort and procedures

Data from 12,265 patients from the three EXPAND studies (**EX**FORGE® in **PA**tie**N**ts with **D**efined risk factors) were analyzed in a meta-analysis. The participants of the first study (EXPAND-O, trial number: CVAA489ADE08) were non-diabetic hypertensive patients with abdominal overweight; the second study (EXPAND-M, trial number: VAA489ADE10) included hypertensive participants with elevated metabolic risk (i.e. patients with at least one metabolic risk factor). The third study (EXPAND-D, trial number: VAA489ADE09) aimed at investigating patients with hypertension and diabetes mellitus.

All three studies had the following objectives: evaluation of BP normalization and/or reaching a target BP individually pre-defined by the treating physician, determination of therapeutic response, evaluation of effectiveness and tolerability as assessed by the treating physician and documentation of incidence and profile of adverse events (AEs) during the observation period (duration 16–24 weeks; Figure 1).

In study EXPAND-O, BP normalization was defined according to WHO criteria (24) for patients with hypertension [systolic BP (SBP) < 140 mmHg and diastolic BP (DBP) < 90 mmHg] and therapeutic response was defined as SBP of < 140 mmHg or at least 20 mmHg decrease vs baseline and DBP of < 90 mmHg or at least 10 mmHg decrease vs baseline.

In study EXPAND-M, BP normalization in patients with hypertension and increased metabolic risk (abnormal fasting glucose/glucose intolerance, type 2 diabetes mellitus, dyslipidemia or abdominal adiposity) was defined as < 140/90 mmHg and < 130/80 in patients with type 2 diabetes mellitus, respectively (according to the Guidelines of the German Hypertension Society; (25)) and as per the ESC/ESH Guidelines (17), the therapeutic response was defined as SBP < 140 mmHg or at least 20 mmHg decrease vs baseline and DBP < 90 mmHg or at least 10 mmHg decrease vs baseline.

In study EXPAND-D, BP normalization was defined according to WHO criteria (17,24) for patients with diabetes mellitus, i.e. an SBP of < 130 mmHg and a DBP of < 80 mmHg. Therapeutic response was defined as SBP of < 130 mmHg or at least 20 mmHg decrease vs baseline and DBP of < 80 mmHg, or at least 10 mmHg decrease vs baseline.

The number of participants of the three studies and the respective study schedules are given in Figure 1.

The three observational multi-center studies aimed to investigate therapy courses and results under routine conditions. Patients were to be treated

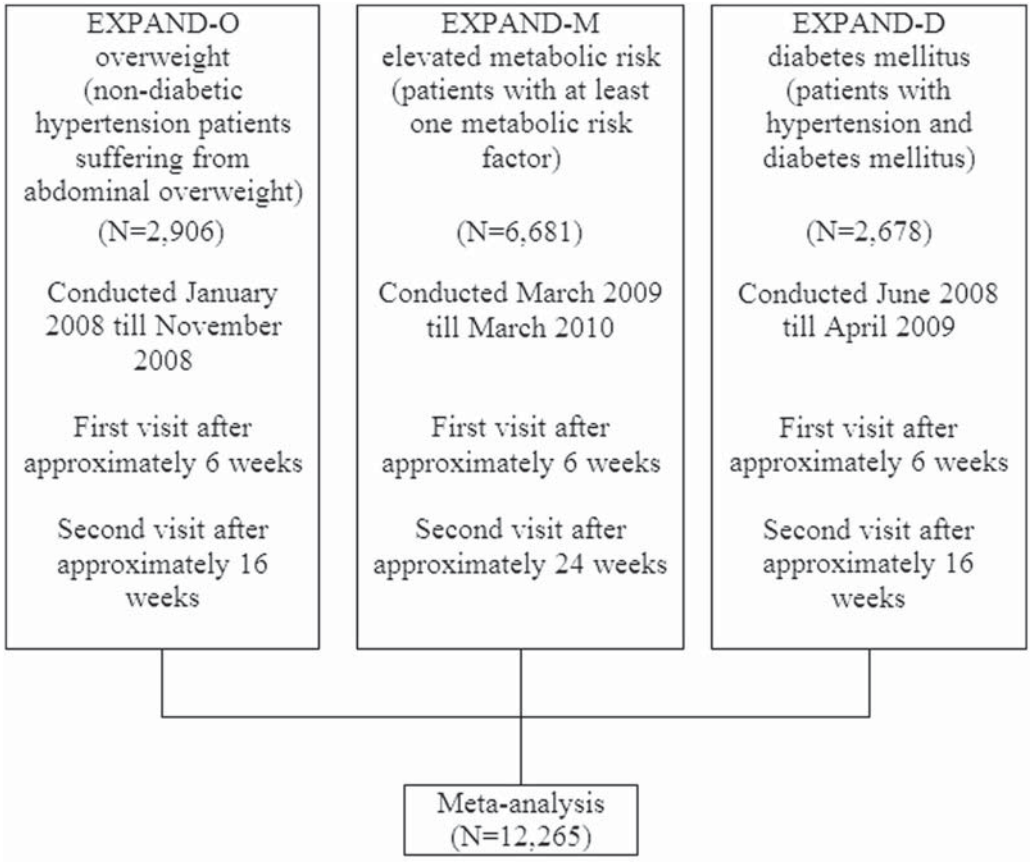

Figure 1. Study schedules and number of participants in the three studies.

only according to medical and therapeutic needs. Based on the principles of non-interventional studies, no directions were given concerning therapy and implementation. The frequency of examinations adhered to practice routine. Additional examinations exceeding the usual extent were not required. Written informed consent for documentation of medical data was obtained.

Data acquisition was conducted between January 2008 and March 2010 with the help of 2440 (581 in EXPAND-O, 1305 in EXPAND-M and 554 in EXPAND-D) general practitioners and internists in Germany. Before the studies were started, approval was obtained from the respective ethics committee. Notification in accordance with § 67 (6) German Drugs Law (AMG) and registration in a publicly accessible registry (VfA) were duly performed.

At the baseline visit, demographic and diagnostic data, metabolic and/or cardiovascular risk factors and relevant prior and concomitant diseases as well as prior and concomitant hypertensive treatment was documented. SBP and DBP, heart rate, amlodipine/valsartan dose, intake and dose of concomitant antihypertensive medication were documented at the start of the study, the optional first control visit (after about 6 weeks) and the final visit (i.e. second control; after 16–24 weeks). Documentation at the final visit included reasons for premature termination, AEs as well as physician's assessment of effectiveness and tolerability and whether patients reached the individually pre-determined target BP.

Data analysis

The database included the respective data of all three EXPAND-studies. Only the subset of variables of identical type and format in all three studies was included. The statistical evaluation was carried out using basic descriptive – and not confirmatory – statistical methods.

The statistical evaluation was carried out using SAS® Version 9.2 for Windows (SAS Institute, Cary, NC).

For qualitative variables, the absolute and relative frequencies were given and for quantitative variables, characteristics of statistical distribution (e.g. mean, median, minimum and maximum) were calculated. Missing data were not censored for analysis, but are not always in the tables. Hence, the total across the respective categories does not always yield 100% for each of the parameters.

To minimize the influence of cases of premature discontinuations and those lost to follow-ups, for each patient the data of the last available visit after start of therapy were used and summed up as a last follow-up (called "last visit").

Results

Patients and demographic characteristics

Baseline characteristics are summarized in Table I. The portion of male patients was slightly higher compared with female patients and the mean age was 63.4 years; 7.4% were aged ≥80 years.

For the majority of the patients, documentation was available for both follow-up visits (76.8%). The first visit took place after a mean of 7.9 weeks (median 6.0 weeks), the second visit after a mean of 19.1 weeks (median 18.0 weeks) and the last visit after a mean of 19.0 weeks (median: 18.0 weeks).

At start of observation the SBP was ≥180 mmHg in 16.7% of patients, ≥160 to <180 mmHg in 45.3% of patients, ≥140 to <160 mmHg in 34.0% of patients, and <140 mmHg in 3.9% of patients. Obesity was present in 41.7% of the patients and 49.0% suffered from type 2 diabetes mellitus.

Table II presents the dosages and their modifications from the start of the study until the last observation. As can be seen, dosage did not remain stable over the course of the study, but an increase in dosage from start of observation to the last visit was apparent: at the beginning, only about one third of the patients received the highest dosage while at the end almost half of the participants were taking the maximal dosage. With regard to dose at last visit, a correlation was observed between the prescribed dose and the normalization and response rates (especially response II): the higher the required daily dose, the lower was the percentage of patients reaching normalization and response.

Blood pressure response

During the course of the observation period, BP decreased markedly (Figure 2). The degree of the reduction was dependent on the BP level at baseline (Figure 3A) as therapy resulted in greater reductions in cases with higher baseline levels.

In contrast to the influence of BP baseline level, differences between age groups (<80 years vs ≥80 years) were negligible (Figure 3B). A similar result was observed for the different BMI strata (Figure 3C). Obviously, BMI exerts no strong influence on the outcome of therapy. Only a slightly greater decrease occurs in SBP for the BMI group <25 kg/m^2. Considering a conceivable influence of diabetes mellitus on the outcome of therapy (Figure 3D), no differences could be observed between the patient groups with or without diabetes.

In Table III, the effects of therapy (normalization of BP value and response of BP value) are listed separately for the different patient characteristics. Regardless of the categorization scheme for BP control, patients with a higher BMI tended to have lower percentages of normalization and response compared with patients with a lower BMI.

Patients with diabetes or prior anti-hypertensive treatment also tended to have lower rates of normalization and response compared with patients without diabetes or patients without prior anti-hypertensive treatment, respectively.

Patients <80 years tended to have higher normalization and response rates than patients ≥80 years.

Individually predefined target blood pressure

The *individually* predefined target BP levels were reached by 62.8% of patients. In cases where the target BP was not reached, the physicians nevertheless stated that for 57.9% of these patients, the BP decrease was satisfactory and in 41.6% they stated that these patients' general condition had definitely improved.

Safety and tolerability

Physicians rated tolerability in 69.3% of the cases as "very good" and in 27.3% as "good". Premature discontinuation of treatment occurred in 3.0% of the cases. The main reasons were AEs (43.4%) and lack of compliance 29.7%.

For 299 of the 12,265 patients (2.44%), a total of 428 AEs (324 non-serious and 104 serious) were recorded. Considering the age groups, 2.38% of the patients <80 years and 3.20% of patients ≥80 years experienced AEs.

In Table IV, the most frequent AEs (i.e. ≥0.05% of patients and more than one patient) are depicted by age group, with edema, dizziness and headache being the most common AEs. SAEs were only seen in 60 patients (0.5%) with most of these being individual occurrences. Largely, no differences were seen between the very elderly patients and patients younger than 80 years of age.

One patient in EXPAND-O died of cancer. No relationship to the study drug was seen. In EXPAND-M, six patients died (events: acute myocardial infarction and ventricular fibrillation, metastases to central nervous system, plasmacytosis, renal failure, neoplasm malignant, myelofibrosis). For the acute myocardial infarction and ventricular fibrillation, the physician assessed the relationship to study drug as unlikely. For the remaining events, no relationship to study drug was seen. Three patients from Study EXPAND-D died. For two of these patients (events: hepatic cancer metastatic; cardiac arrest, cerebrovascular insufficiency, cerebrovascular accident), no causal relationship to study treatment was seen by the study physician. For the third case (event: glioblastoma), the sponsor's medical expert (in the absence of the physician's assessment) saw no relationship to study treatment.

Table I. Demographic and baseline parameters.

	Number (%) or mean ± SD	Median
Gender		
Male	6544 (53.4)	
Female	5429 (44.3)	
Age (years)	63.4 ± 11.7	63.7
Age categorization		
< 80 years	11,172 (91.1)	
≥ 80 years	905 (7.4)	
Height (cm)	170.8 ± 9.2	170.0
Weight (cm)	87.4 ± 16.3	86.0
BMI (kg/m^2)	29.9 ± 4.9	29.1
BMI categories		
Missing	180 (1.5)	
Normal body weight (< 25 kg/m^2)[a]	1414 (11.5)	
Pre-adiposity (≥ 25 and < 30 kg/m^2)	5555 (45.3)	
Adiposity (≥ 30 kg/m^2)	5116 (41.7)	
Systolic blood pressure at study start	162.3 ± 16.0	160.0
Systolic blood pressure (categories) at study start		
Missing	14 (0.1)	
< 140 mmHg	478 (3.9)	
≥ 140 and < 160 mmHg	4170 (34.0)	
≥ 160 and < 180 mmHg	5554 (45.3)	
≥ 180 mmHg	2049 (16.7)	
Diastolic blood pressure at study start	93.5 ± 9.8	95.0
Diastolic blood pressure (categories) at study start		
Missing	11 (0.1)	
< 80 mmHg	513 (4.2)	
≥ 80 and < 90 mmHg	2297 (18.7)	
≥ 90 and < 100 mmHg	5342 (43.6)	
≥ 100 and < 110 mmHg	3269 (26.7)	
≥ 110 mmHg	833 (6.8)	
Essential hypertension		
Yes	12,178 (99.3)	
No	87 (0.7)	
Duration of essential hypertension (years)	8.2 ± 6.7	7.1
Duration of essential hypertension (years) categories		
Missing	605 (5.0)	
< 1 year	1341 (11.0)	
≥ 1 and < 5 years	3044 (25.0)	
≥ 5 and < 10 years	3587 (29.5)	
≥ 10 years	3601 (29.6)	
Waist circumference (cm)	106.4 ± 13.7	105.0
Cardiovascular risk factors (most common)		
Total	12,265 (100.0)	
Dyslipidemia	8364 (68.2)	
Positive family anamnesis	6809 (55.5)	
Diabetes mellitus	6005 (49.0)	
Smoker	3446 (28.1)	
Coronary heart disease	2571 (21.0)	
Left ventricular hypertrophy	2551 (20.8)	
Congestive heart failure	1498 (12.2)	
Microalbuminuria	1233 (10.1)	
Antihypertensive pretreatment		
Yes	10,482 (85.5)	
No	1576 (12.8)	
Prior medication for essential hypertension (most common)		
ACE inhibitors, plain	3872 (36.9)	
Angiotensin II antagonists and diuretics	1358 (13.0)	
Angiotensin II antagonists, plain	1427 (13.6)	
Beta blocking agents, selective	3241 (30.9)	
Dihydropyridine derivatives	3154 (30.1)	
Thiazides, plain	1060 (10.1)	
Number of prior antihypertensive medications		
Total	10,482 (100.0)	
Prior medication not specified	273 (2.6)	
One antihypertensive drug medication	4789 (45.7)	
Two antihypertensive drugs	3336 (31.8)	
Three antihypertensive drugs	1625 (15.5)	
Four antihypertensive drugs	335 (3.2)	
More than four antihypertensive drugs medications	124 (1.2)	

ACE, angiotensin-converting enzyme. [a]Includes 11 patients with a BMI of ≤ 18.5 kg/m^2.

Table II. Treatment with single-pill combination of amlodipine/valsartan – daily dose.

Daily dose of aml/val (mg)	Start of observation		6 weeks		16–24 weeks		Last visit	
	n	%	*n*	%	*n*	%	*n*	%
Total	12,265	100.0	9537	100.0	12,097	100.0	12,212	100.0
Missing	17	0.1	219	2.3	171	1.4	189	1.5
5 mg/80 mg	1840	15.0	795	8.3	1118	9.2	1126	9.2
5 mg/160 mg	5988	48.8	4083	42.8	4959	41.0	5003	41.0
10 mg/160 mg	4420	36.0	4440	46.6	5849	48.4	5894	48.3

Discussion

The present report summarizes results of three large-scale observational studies, carried out in Germany, dealing with antihypertensive therapy with a single-pill combination of amlodipine/valsartan. The antihypertensive efficacy of combinations of once-daily amlodipine/valsartan has been demonstrated in several large, randomized, double-blind clinical trials of 8–16 weeks' duration. BP reductions were maintained for approximately 1 year in open-label extensions of some of these studies (26).

In our meta-analysis, we particularly took into consideration the influences of specific patient characteristics, i.e. age, presence/absence of diabetes mellitus, and BMI. BP reduction, in general, was pronounced.

After 6 weeks, SBP decreased by 20.8 mmHg, DBP by 9.8 mmHg. The corresponding values after 16–24 weeks being 28.5 mmHg and 13.5 mmHg, respectively. These observations under practice conditions are in the same range as those observed in clinical trials: for instance, in the study by Philipp and colleagues (27), hypertensive patients with a DBP between ≥ 95 mmHg and < 110 mmHg were investigated. BP at baseline was 153/99 mmHg. Amlodipine/valsartan in doses of 5/80 mg, 5/160 and 5/320 mg lowered BP by 20–23/14–16 mmHg.

In clinical practice, physicians are frequently confronted with hypertensive patients of higher age and/or patients suffering from additional health problems like obesity and diabetes mellitus. BP rises steadily with age, so that lowering of BP becomes more and more important in the elderly. Several large-scale trials have proved the positive effects of antihypertensive therapy in the prevention of cardiovascular diseases in elderly patients (12,28). The latest developments in the treatment of hypertension suggest aiming for a reduction of SBP below 150 mmHg in patients aged ≥ 80 years [Guidelines of the German Hypertension Society (29)] and stipulate that this reduction should be approached with caution, taking into account the individual patient's state of health. This is in line with results of the HYVET trial (12).

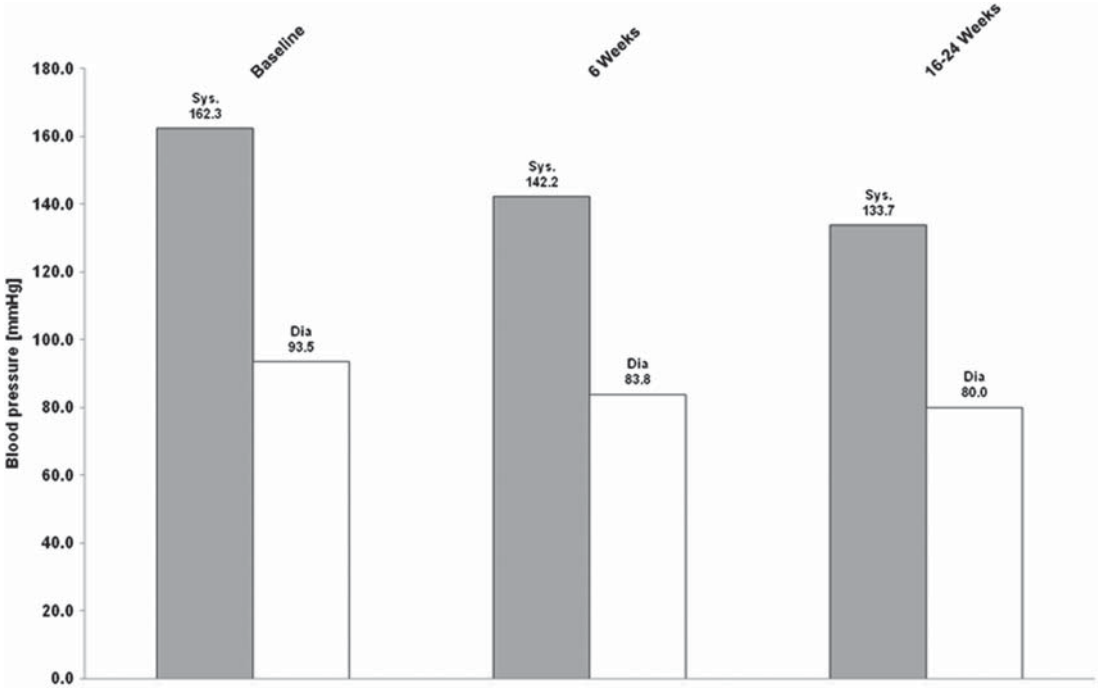

Figure 2. Time course of systolic and diastolic blood pressure – mean values.

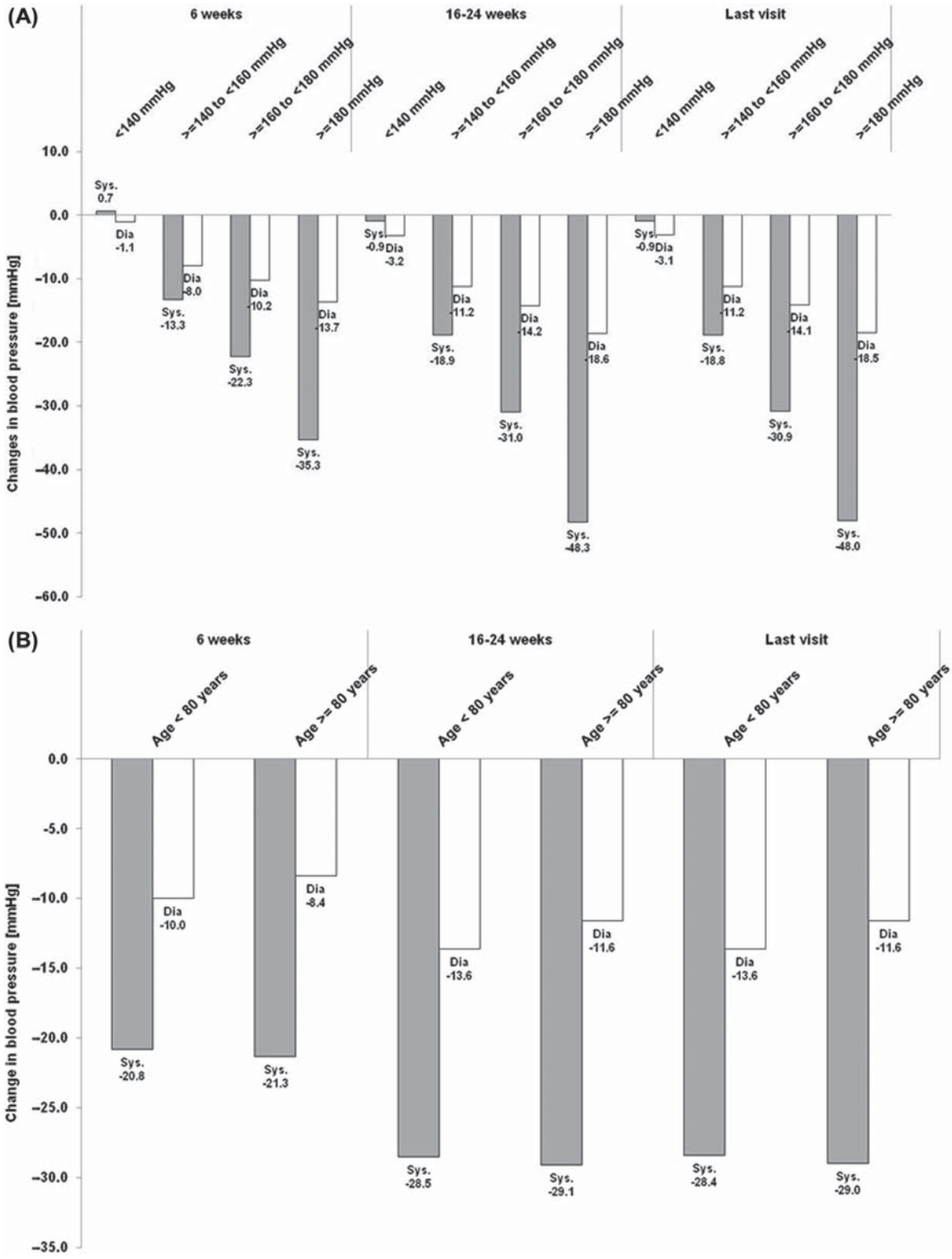

Figure 3. Changes in blood pressure from baseline: (A) stratification by systolic blood pressure at baseline – mean values; (B) stratification by age – mean values; (C) stratification by body mass index (BMI) – mean values; (D) stratification by diabetes mellitus status.

Our data provides evidence for an equivalent BP reduction, regardless of age group, even if patients above the age of 80 are considered. Within this context, it can be assumed that an important contribution to the effectiveness of amlodipine/valsartan in the (very) elderly may be the single-pill combination of the two compounds. In this age group, compliance with therapy is a major concern due, among other things, to polypharmacotherapy and forgetfulness. As has been shown, single-pill combinations can significantly increase adherence to a drug regimen, particularly so for elderly patients (30,31).

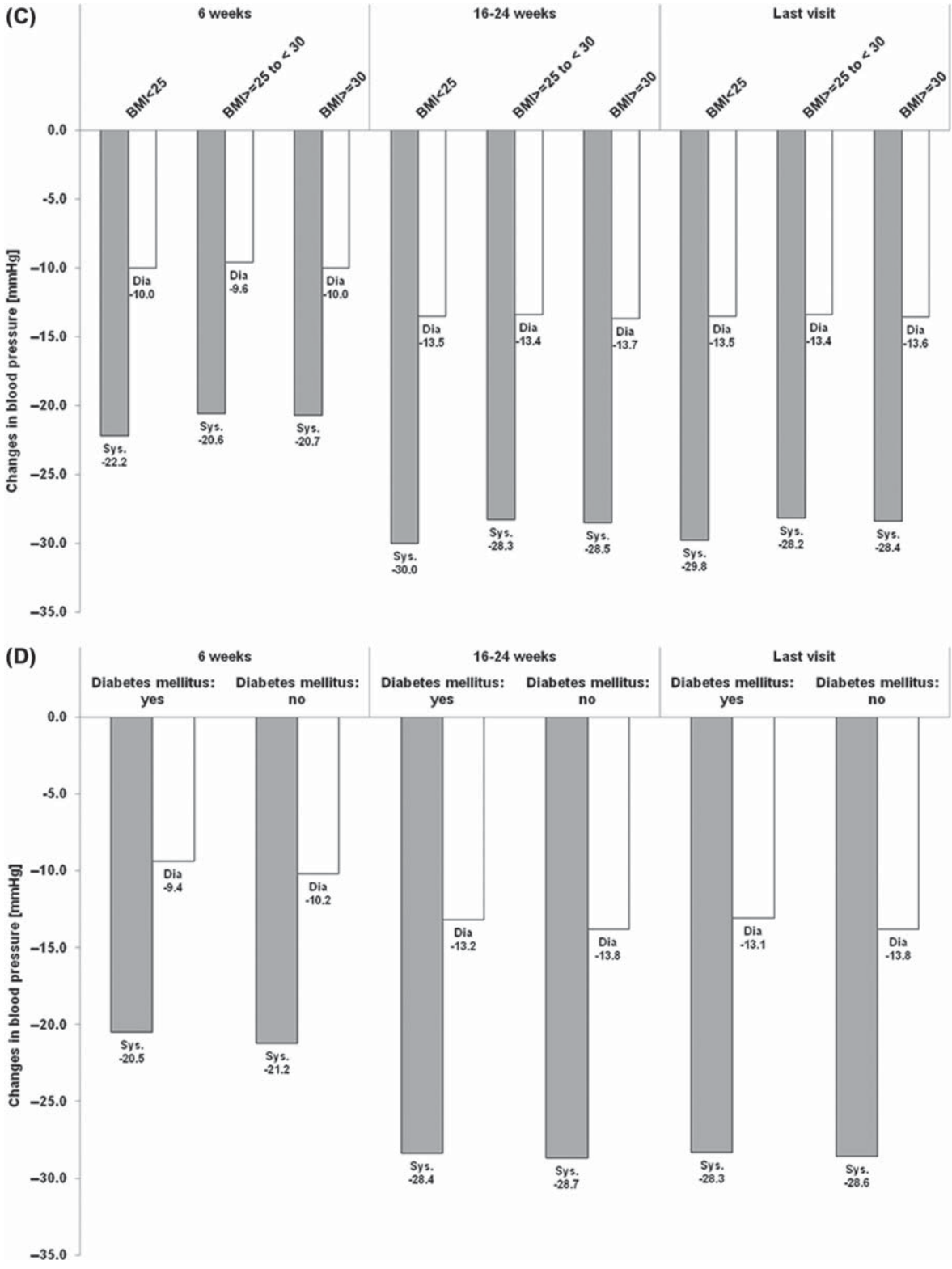

Figure 3.(*Continued*).

The prevalence and severity of hypertension increases with an increasing BMI (32). Since obesity is characterized by various hemodynamic and metabolic abnormalities, including an increase in circulating blood volume and systemic vascular resistance, the development of hypertension is a common consequence. In our sample a total of 87% of the participants were characterized by pre-adiposity (45.3%) or adiposity (41.7%). Thus, the effectiveness of an antihypertensive drug for this large patient group is of major importance. It could be demonstrated that the three BMI groups < 25 kg/m^2, ≥ 25 to < 30 kg/m^2, and ≥ 30 kg/m^2 did not differ markedly in SBP as well as DBP reduction. Only a slightly

Table III. Normalization of blood pressure and response at last control.

	Normalization		Response I[a]		Response II[b]	
	n	(%)	*n*	(%)	*n*	(%)
Total	4740	38.8	9273	75.9	6390	52.3
Aml/val – dose at last control						
5 mg/80 mg	556	49.4	895	79.5	714	63.4
5 mg/160 mg	2113	42.2	3844	76.8	2826	56.5
10 mg/160 mg	2024	34.3	4424	75.1	2789	47.3
Body mass index						
<25 kg/m^2	552	44.5	971	78.3	709	57.2
≥ 25 kg/m^2 to <30 kg/m^2	2135	41.2	3981	76.7	2877	55.5
≥ 30 kg/m^2	1812	36.7	3716	75.2	2406	48.7
Diabetes mellitus						
Yes	1018	17.0	4046	67.6	2999	50.1
No	3722	59.8	5227	84.0	3391	54.5
Prior anti-hypertensive treatment						
Yes	3973	38.0	7808	74.8	5428	52.0
No	693	44.3	1318	84.2	859	54.9
Systolic blood pressure at start of observation						
<140 mmHg	237	53.3	248	55.7	219	49.2
≥ 140 to <160 mmHg	1917	48.7	2589	65.8	2340	59.4
≥ 160 to <180 mmHg	1883	36.1	4248	81.4	2728	52.3
>180 mmHg	503	26.4	1673	87.8	774	40.6
Diastolic blood pressure at start of observation						
<90 mmHg	1239	44.4	1608	57.6	1447	51.8
≥ 90 mmHg	3499	37.2	7663	81.4	4942	52.5
Age						
<80 years	4375	39.3	8455	76.0	5828	52.4
≥ 80 years	300	33.4	671	74.7	466	51.9

For definition of normalization, see methods section. [a]Response I = therapeutic response (in EXPAND-M and EXPAND-O therapeutic response was defined as systolic blood pressure <140 mmHg or at least 20 mmHg decrease vs baseline and diastolic blood pressure <90 mmHg or at least 10 mmHg decrease vs baseline, while in EXPAND-D therapeutic response was defined as systolic blood pressure <130 mmHg or at least 20 mmHg decrease vs baseline and diastolic blood pressure <80 mmHg or at least 10 mmHg decrease vs baseline). [b]Response II = reached target blood pressure defined by treating physician.

greater reduction in SBP (about 2 mmHg) for the BMI group <25 kg/m^2 occurred.

Hypertension is one of the major risk factors for adverse outcomes in patients with type 2 diabetes mellitus and a most important target for intervention (33,34). Thus, the effectiveness of a BP lowering drug for this patient group is most important. In our subsample of diabetic patients, the therapeutic response (defined as SBP <130 mmHg or at least 20 mmHg decrease vs baseline and DBP <80 mmHg or at least 10 mmHg decrease vs baseline) was observed in 67.6% of the patients.

Table IV. Most frequently reported adverse events (≥ 0.05% of patients and more than 1 patient) – by age group.

	Total, $n=12{,}265$		<80 years, $n=11{,}172$		≥ 80 years, $n=905$	
	n	%	*n*	%	*n*	%
Edema peripheral	116	0.95	104	0.93	11	1.22
Edema	22	0.18	19	0.17	3	0.33
Dizziness	13	0.11	13	0.12	0	0.00
Headache	11	0.09	11	0.10	0	0.00
Flushing	10	0.08	9	0.08	1	0.11
Pruritus	8	0.07	8	0.07	0	0.00
Cough	7	0.06	7	0.06	0	0.00

This result may, for example, be contrasted to an observation of the INSIGHT study (3), where patients with diabetes were the most resistant to treatment, requiring second and third drugs much more frequently than patients without diabetes.

Being based on a meta-analysis of three observational studies, the presented data have the typical methodological limitations of observational studies. The heterogeneity of the patient population can include a wide variation of patient's diseases and disease severity. Data may sometimes be inconsistent and incomplete as patients are lost to follow-up during the observation period. To minimize the influence of premature discontinuations and "lost to follow-up" cases on the results, the data of the last available visit after start of therapy were also used and summed up as a last follow-up (called "last visit").

Additionally, no specific schedule for the measurements (in this case the BP measurements) is preset according to which the physicians need to perform their BP measurements. Another often discussed weakness of an observational study and in fact of every non-randomized study is that there may be a selection bias due to the lack of blinding and randomization. This may be caused by the fact that the

treating physician chooses which patients will be treated with which medication.

However, a major strength of the results presented is the large number of patients, which was achieved by analyzing data of three trials together in a meta-analysis and which provided a sufficiently large sample size to allow for analysis of differences between the subgroups.

In summary, the regimen with the single-pill combination therapy with amlodipine/valsartan in daily practice has a favorable safety profile and tolerability, as already seen in clinical studies. Based on these results, it offers a rational and convenient treatment option for the management of patients with hypertension, the majority of whom will require at least two drugs to reach target BP levels as recommended by US (and international) guidelines.

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The authors acknowledge the cooperation of the patients, investigators and staff at all participating sites of this study.

Conflicts of interest: S. Eckert has received honoraria for lectures from Novartis Pharma GmbH; he was the principal investigator for EXPAND-D. S. Freytag is employed by Kantar Health GmbH, which conducted the studies and the analysis on behalf of Novartis Pharma GmbH. A. Müller and S. Klebs are employees of Novartis Pharma GmbH.

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References

1. Whitworth JA. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens. 2003;21:1983–1992.
2. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss. Arterioscler Thromb Vasc Biol. 2006;26:968–976.
3. Brown CD, Higgins M, Donato KA, Rohde FC, Garrison R, Obarzanek E, et al. Body mass index and the prevalence of hypertension and dyslipidemia. Obes Res. 2000;8:605–619.
4. Ernst ND, Obarzanek E, Clark MB, Briefel RR, Brown CD, Donato K. Cardiovascular health risks related to overweight. J Am Diet Assoc. 1997;97:S47–S51.
5. Krauss RM, Winston M, Fletcher BJ, Grundy SM. Obesity: Impact on cardiovascular disease. Circulation. 1998;98:1472–1476.
6. Pimenta E, Oparil S. Management of hypertension in the elderly. Nat Rev Cardiol. 2012;9:286–296. doi:10.1038/nrcardio. 2012.27.
7. Banach M, Aronow WS. Should we have any doubts about hypertension therapy in elderly patients? ACCF/AHA 2011 expert consensus document on hypertension in the elderly. Pol Arch Med Wewn. 2011;121:253–258.
8. Gil-Extremera B, Cia-Gomez P. Hypertension in the elderly. Int J Hypertens. 2012;859176. Epub 2011 Aug 16.
9. Virdis A, Bruno RM, Neves MF, Taddei S, Ghiadoni L. Hypertension in the elderly: An evidence-based review. Curr Pharm Des. 2011;17:3020–2031.
10. Mitka M. New guidance covers ways to prevent and treat hypertension in elderly patients. JAMA. 2011;305:2394–2398.
11. Schall P, Wehling M. Treatment of arterial hypertension in the very elderly: A meta-analysis of clinical trials. Arzneimittelforschung. 2011;61:221–228.
12. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887–1898.
13. Bulpitt CJ, Beckett NS, Cooke J, Dumitrascu DL, Gil-Extremera B, Nachev C, et al. Results of the pilot study for the Hypertension in the Very Elderly Trial. J Hypertens. 2003;21:2409–2417.
14. Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekbom T, Fagard, R et al. Antihypertensive drugs in very old people: A subgroup meta-analysis of randomised controlled trials. INDANA Group. Lancet. 1999;353:793–796.
15. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 1991;265:3255–3264.
16. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997;350:757–764.
17. Mancia G, De BG, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2007;25:1105–1187.
18. da Silva PM. Efficacy of fixed-dose combination therapy in the treatment of patients with hypertension: Focus on amlodipine/valsartan. Clin Drug Investig. 2010;30:625–641.
19. Flack JM, Hilkert R. Single-pill combination of amlodipine and valsartan in the management of hypertension. Expert Opin Pharmacother. 2009;10:1979–1994.
20. Fogari R, Zoppi A, Derosa G, Mugellini A, Lazzari P, Rinaldi A, et al. Effect of valsartan addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. J Hum Hypertens. 2007;21:220–224.
21. Lemmer B, Middeke M, Schaaf B, Eckes L. Prescribing practices and morning blood pressure control: Results of a large-scale, primary-care study conducted in Germany. J Hum Hypertens. 2008;22:295–297. Epub 2008 Jan 17.
22. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA. 2003;289:2363–2369.
23. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, et al. Hypertension treatment and control in five European countries, Canada, and the United States. Hypertension. 2004;43:10–17.

24. Guidelines Subcommittee. World Health Organization–International Society of Hypertension guidelines for the management of hypertension. J Hypertens. 1999;17:151–183.
25. Deutsche Hochdruckliga e.V. DHL® – Deutsche Hypertonie Gesellschaft: Leitlinien zur Behandlung der arteriellen Hypertonie, status of 1 June 2008.
26. Frampton JE, Scott LJ. Amlodipine/valsartan single-pill combination: A review of its use in the management of hypertension. Am J Cardiovasc Drugs. 2009;9:309–330.
27. Philipp T, Smith TR, Glazer R, Wernsing M, Yen J, Jin J, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Clin Ther. 2007;29:563–580.
28. Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Schersten B, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: Cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet. 1999;354:1751–1756.
29. Deutsche Hochdruckliga e.V. DHL® – Deutsche Hypertonie Gesellschaft: Neue Entwicklungen in der Hochdruckthe-rapie; 2011.
30. Bangalore S, Shahane A, Parkar S, Messerli FH. Compliance and fixed-dose combination therapy. Curr Hypertens Rep. 2007;9:184–189.
31. Dickson M, Plauschinat CA. Compliance with antihypertensive therapy in the elderly: A comparison of fixed-dose combination amlodipine/benazepril versus component-based free-combination therapy. Am J Cardiovasc Drugs. 2008;8: 45–50.
32. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: Risk factor, paradox, and impact of weight loss. J Am Coll Cardiol. 2009;53:1925–1932.
33. Thomas M C, Atkins RC. Blood pressure lowering for the prevention and treatment of diabetic kidney disease. Drugs. 2006;66:2213–2234.
34. Thomas MC, Atkins R. Assessment and management of hypertension in patients with type 2 diabetes. Intern Med J. 2009;39:143–149.