Effectiveness of Indapamide/amlodipine Single-pill Combination in Patients With Isolated Systolic Hypertension: Post-hoc Analysis of the ARBALET Study

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Research Article

Keywords: indapamide/amlodipine single-pill combination, combination therapy, isolated systolic hypertension

DOI: https://doi.org/10.21203/rs.3.rs-125731/v1

Abstract

Background: Isolated systolic hypertension (ISH) is a major cause of morbidity and mortality. This study evaluated the effectiveness of treatment with an indapamide/amlodipine single-pill combination (SPC) in outpatients with uncontrolled ISH aged over 55 years in real-life clinical practice.

Methods: This was a post-hoc analysis of the subgroup of patients with ISH from ARBALET, a 3-month, multicenter, observational, open-label study conducted in Russia among patients with grade I or II hypertension who were either uncontrolled on previous antihypertensive treatment or treatment-naïve. The effectiveness of indapamide/amlodipine SPC was assessed by the change in office systolic blood pressure (SBP) and the rate of target SBP (<140 mmHg) achievement at 2 weeks, 1 month and 3 months, in four age groups: 55-59 years, 60-69 years, 70-79 years, and 80 years or older.

Results: The ARBALET study recruited 2217 patients, of whom 626 had ISH and were included in this post-hoc analysis (mean age 66.1±7.8 years; 165 men [26.36%] and 461 women [73.64%]). Target SBP <140 mmHg was achieved in 43%, 75% and 93% of patients at 2 weeks, 1 and 3 months, respectively. SBP decreased from baseline by 18.8±10.5 mmHg, 27.2±10.6 mmHg and 31.8±9.9 mmHg at 2 weeks, 1 month and 3 months, respectively. In the groups of patients aged 55-59, 60-69, 70-79, and ≥80 years, SBP reductions at 3 months compared with baseline were -30.3±9.4, -32.4±9.7, -32.5±10.7, and -28.9±9.6 mmHg, respectively.

Conclusion: This post-hoc analysis of the observational ARBALET study showed that indapamide/amlodipine SPC was associated with significant reductions in BP and high rates of target BP achievement in a broad age range of patients with ISH treated in routine clinical practice.

Trial registration number: ISRCTN40812831

Introduction

Isolated systolic hypertension (ISH) is defined as a systolic blood pressure (SBP) ≥ 140 mmHg with a diastolic blood pressure (DBP) < 90 mmHg [1, 2]. There is a linear increase in both SBP and DBP up to around 45 years in men and 55 years in women after which the prevalence of ISH begins to increase [3, 4]. In the NHANES III study, the proportion of those with ISH among all hypertensive patients aged 45–54 years was 24%, among 55-64-year olds it was 47%, among 65-74-year olds it was 66%, and in over 75-year olds it was 73% [5]. In men, prevalence rises from 5.1% at the age of 25–34 years to 23.6% at the age of 65–74 years, and in women from 2.7–20.4% in the same age groups [5]. ISH is associated with a two- to fourfold increase in the risk of myocardial infarction (MI), left ventricular hypertrophy (LVH), renal dysfunction, stroke, and cardiovascular death [4]. In the Physician's Health Study of apparently healthy men aged 40–84 years, even borderline ISH significantly increased the risk of cardiovascular disease by 32%, stroke by 42%, cardiovascular death by 56% and all-cause mortality by 22% 6]. The debate on whether "to treat or not to treat hypertension, including ISH in the elderly" is therefore a thing of the past.

A major factor contributing to the rise in SBP and fall in DBP with increasing age is large artery stiffening, which limits arterial distension when pressure is exerted on the arterial wall. An increase in SBP, while maintaining the level of DBP, results in an increased pulse pressure (PP), defined as the difference between SBP and DBP which has a normal range of 30 to 50 mmHg. The relationship between increased PP, arterial stiffness and aging has been repeatedly confirmed in epidemiological studies [7]. Both the Framingham study and National Health and Nutrition Examination Survey (NHANES) have demonstrated an increase in SBP and decrease in DBP after the age of 60, both in patients with normal BP and in patients with untreated hypertension [8]. PP measurement can be considered a surrogate method for assessing the stiffness of elastic central arteries [7], and a value ≥ 60 mmHg in elderly persons was added to the list of asymptomatic hypertension-mediated organ damage in the latest European guidelines for the management of arterial hypertension [1, 9].

In addition to increased arterial stiffness, hypertension in older patients is influenced by a number of other features that should be considered when selecting treatment options, including circadian rhythm disturbances, high BP variability, and reduced plasma renin activity leading to the development of sodium-volume dependent hypertension. Furthermore, in a high proportion of patients, antihypertensive therapy is associated with suboptimal rates of target BP achievement [10].

Achieving BP control is essential for the improvement of hypertension-related outcomes, and often requires prescription of a combination of antihypertensive agents with different mechanisms of action. A single-pill combination (SPC) is the preferred method of administration as it reduces the pill burden and can improve treatment adherence [1].

In 2017, a unique SPC combining the thiazide-like diuretic indapamide sustained release at a dose of 1.5 mg with the calcium channel blocker (CCB) amlodipine at a dose of 5 or 10 mg was registered in Russia.

The ARBALET study [11] was designed to evaluate the antihypertensive effectiveness and tolerability of the indapamide/amlodipine SPC in patients with hypertension over 55 years of age in real clinical practice. The results showed that 90% of patients achieved target BP level by the third month of treatment and that the number of patients with a PP < 60 mmHg increased from 7.8–82%. Herein, we present a post-hoc analysis of the ARBALET study whose aim was to assess the effectiveness of treatment with indapamide/amlodipine SPC specifically in outpatients with ISH.

Methods

Study design

ARBALET was a 3-month, multicenter, open-label, observational, uncontrolled study, conducted between November 2017 and March 2018. A total of 730 physicians from 57 regions of the Russian Federation enrolled 2217 patients. The methods and main findings of the ARBALET study have been previously published in Russian [11]. Briefly, eligible patients were aged ≥ 55 years, had primary hypertension

diagnosed at least 3 months before inclusion in the study, had uncontrolled BP on previous antihypertensive therapy (office SBP 140–179 mm Hg), or were antihypertensive treatment-naïve patients with grade I or II hypertension or with PP ≥ 60 mmHg. Patients were divided into four age groups: 55–59, 60–69, 70–79, and 80–90 years. Exclusion criteria included: an office BP ≥ 180/110 mmHg despite antihypertensive treatment (at inclusion visit) or ≥ 200/110 mmHg if antihypertensive treatment-naïve; resistant hypertension (use of 3 antihypertensive drugs of different classes at the best tolerated doses, one of which must be a diuretic); a history of myocardial infarction, unstable angina, or cerebrovascular accident within the prior 6 months; New York Heart Association (NYHA) class III or IV chronic heart failure (CHF); type 1 diabetes mellitus (DM) or decompensated type 2 DM; any severe decompensated concomitant diseases; inability to understand the nature of the program and follow the recommendations; contraindications or known intolerance to diuretics and CCB (including indapamide and amlodipine); or participation in any other clinical study within 30 days prior to the program.

Each treating physician selected three or more consecutive patients who met the above criteria and, in his/her opinion, required an adjustment of their antihypertensive therapy. The adjustment could constitute either the addition of indapamide/amlodipine SPC to previous therapy, or replacement of the effective free combination of the same agents with the SPC. The indapamide/amlodipine SPC dose was selected by the physician from two available options (indapamide/amlodipine 1.5/5 mg or 1.5/10 mg). In all cases, treatment was prescribed in accordance with the instructions for use of the drugs, after the patient had signed an informed consent form.

The study included three pre-scheduled patient visits at 2 weeks, 1 and 3 months after the inclusion visit. At each visit, the physician measured BP and heart rate (HR) and completed the case report form. A diary of BP self-monitoring, completed by the patient in the 7 days prior to the physician visit, was also analysed. Based on the obtained data, a decision concerning treatment continuation was made by the physician and the dose of drug was titrated at the 2 week or 1 month visits, if necessary. Adverse events were monitored throughout the study. After recording the timings of previous drug intake and BP measurements, BP was measured in the physician's office using the Korotkoff' technique. With the patient in a sitting position, BP was measured on the right arm after 5 minutes of rest. BP and HR were measured three times at 1- to 2-minute intervals, and the mean value of the last two measurements was registered.

The primary efficacy endpoints were change in SBP and DBP values at the final visit *versus* baseline (recorded at the inclusion visit), and rate of target BP achievement. Secondary efficacy endpoints in this subgroup of patients with ISH included the rates of target SBP (< 130 mmHg) and PP (< 60 mmHg) achievement.

Statistical analysis

All parameters were analysed using descriptive statistics methods. Changes in mean SBP and DBP values (with corresponding 95% confidence intervals [CI]) were evaluated in the per-protocol population. To assess the differences in the normally distributed parameters, the Student's t-test for paired measurements was used; the Wilcoxon nonparametric rank-sum test was used for parameters that were

not normally distributed. The proportions (with corresponding 95% CI) of patients achieving target BP, as well as those who responded to treatment were also calculated.

Compliance with ethics guidelines

All diagnostic procedures were performed after written informed consent had been provided by the patient. The study was conducted in accordance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. The study protocol was approved by the Peoples' Friendship University of Russia (RUDN University.

Results

Patient demographics

The primary ARBALET study population comprised 2217 patients. Mean age was 64.2 ± 7.4 years and 692 (31.2%) were men. Mean baseline SBP was 161.7 ± 10.3 mmHg and mean DBP was 90.7 ± 9.7 mmHg. Prior to inclusion in the study 28.0% of patients were being prescribed antihypertensive monotherapy, 38.7% were receiving two antihypertensive agents, 15.0% three agents, 4.2% four agents, and 0.5% of patients were receiving five antihypertensive agents. At study entry, 68.5% were prescribed indapamide/amlodipine SPC at a dose of 1.5/5 mg and 31.5% were prescribed a dose of 1.5/10 mg. The proportion of patients receiving the two different SPC doses at each study visit is shown in Fig. 1. The number of concomitant drugs taken by patients before inclusion in the program had an influence on the prescribed SPC dose. For most patients (96.5%), the SPC dose remained stable during the study. At 3 months, 60.7% of patients were receiving a dose of 1.5/5 mg, and 39.3% were receiving 1.5/10 mg. In a small number of patients some dose changes were noted, which mainly consisted of a dose increase at the final visit in 2.0% of patients (Table 1).

Table 1
Change in the daily dose of the study drug during therapy.

	Proportion of patients (%) with dose titrated at each study visit		
	2 weeks	1 month	3 months
No change	99.7	91.1	96.5
Dose reduced	0.2	0.9	1.5
Dose increased	0.1	8.0	2.0

The remainder of this paper focuses on the post-hoc analysis population of 626 patients in the ARBALET study who presented with ISH. Baseline patient characteristics in the ISH population were similar to those of the main population [11] except for a greater proportion of patients aged 70 to 79 years of age (27.3% vs 19.6%) and a higher mean age (66.1 ± 7.8 vs 64.2 ± 7.4 years). Among the ISH population there were

165 (26.4%) men and 461 (73.6%) women. The main clinical and demographic characteristics of the ISH patients are presented in Table 2. Mean baseline SBP was 159.2 ± 8.7 mmHg, DBP was 79.7 ± 6.5 mmHg, PP 79.5 ± 10.7 mmHg, and HR 71.7 ± 8.0 beats per minute. Analysis of cardiovascular risk factors showed that more than two-thirds of patients had dyslipidemia (n = 434 patients; 69.3%) and more than half had abdominal obesity (n = 348; 55.6%). The most prevalent concomitant diseases/conditions were echocardiographically-confirmed LVH (n = 455; 72.7%), CAD (n = 208; 33.2%), and CHF (n = 276; 44.1%).

Table 2
Baseline characteristics of patients with ISH (n = 626)

Parameter	Value
Men, n (%)	165 (26.4)
Women, n (%)	461 (73.6)
Age, years, mean ± SD	66.1 ± 7.8
55–59 years, n (%)	137 (21.9)
60–69 years, n (%)	281 (44.9)
70–79 years, n (%)	171 (27.3)
≥ 80 years, n (%)	30 (4.8)
Risk factors	
Current smoker, n (%)	103 (16.5)
Dyslipidemia, n (%)	434 (69.3)
Fasting plasma glucose ≥ 5.6 mmol/L, n (%)	146 (23.3)
Abdominal obesity, n (%)	348 (55.6)
Family history of CVD, n (%)	160 (25.6)
Concomitant diseases and conditions	
Confirmed LVH, n (%)	455 (72.7)
Proteinuria, n (%)	34 (5.4)
CAD, n (%)	208 (33.2)
Stable angina, n (%)	138 (22.0)
History of myocardial infarction, n (%)	40 (6.4)
History of coronary revascularisation, n (%)	29 (4.6)
History of stroke or TIA, n (%)	23 (3.7)
Peripheral artery disease, n (%)	83 (13.3)
Class I or II CHF, n (%)	276 (44.1)
Type 2 diabetes mellitus, n (%)	72 (11.5)
COPD/asthma, n (%)	37 (5.9)

Abbreviations: CAD: coronary artery disease; CHF: chronic heart failure; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; LVH: left ventricular hypertrophy, ISH: isolated systolic hypertension; SD: standard deviation; TIA: transient ischemic attack.

At baseline, all participants were prescribed an indapamide/amlodipine SPC, which replaced previous antihypertensive treatment in 460 (73.5%) patients, was added to a current antihypertensive regimen in 80 (12.8%) patients, and was initiated in 86 (13.7%) treatment-naïve patients with ISH. The 1.5/5 mg dose was prescribed in 466 (74.4%) patients and the 1.5/10 mg dose in 160 (25.6%).

Concomitant treatments

A total of 540 out of 626 patients (86.3%) had received previous antihypertensive treatment and 86 were treatment naïve. Previous antihypertensive agents included angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), beta-blockers, CCB, diuretics, and imidazoline receptor agonists. Of the 540 on previous antihypertensive treatment 175 (32.4%) were receiving monotherapy and 365 (67.6%) were receiving combination therapy prescribed as either a free combination (n = 305; 83.6%) or as a SPC (n = 60; 16.4%).

A proportion of patients received concomitant antihypertensive therapy during the study in addition to the indapamide/amlodipine SPC including ACE inhibitors in 174 patients (27.8%), ARB in 102 (16.3%), beta-blockers in 210 (33.6%), CCB in 3 (0.5%), diuretics in 12 (1.9%), and imidazoline receptor agonists in 10 (1.6%) patients (Fig. 2).

Changes in SBP levels

BP measurements were available for 615 (98.2%) patients who completed the study in accordance with the study protocol. Statistically significant reductions compared with baseline were observed for SBP, DBP and PP from Week 2 and remained significant for the duration of the study (Table 3, Fig. 3). Changes in SBP levels by age group are presented in Fig. 4. After 3 months of treatment with the indapamide/amlodipine SPC, significant SBP decreases from baseline were observed in each age group: -30.3 ± 9.4 mmHg (from 156.8 ± 8.4 to 126.5 ± 7.3), -32.4 ± 9.7 mmHg (from 159.1 ± 8.5 to 126.6 ± 7.1), -32.5 ± 10.7 mmHg (from 161.2 ± 8.9 to 128.7 ± 7.7), and − 28.9 ± 9.6 mmHg (from 159.3 ± 8.5 to 130.5 ± 7.1) in the 55–59, 60–69, 70–79, and 80 years and older age groups, respectively.

Table 3
BP decrease during the study.

Parameter	Baseline	Week 2	Month 1	Month 3
SBP, mm Hg, mean ± SD	159.2 ± 8.7	140.4 ± 11.0*	132.0 ± 9.5*	127.3 ± 7.4*
DBP, mm Hg, mean ± SD	79.7 ± 6.5	76.5 ± 6.8*	74.3 ± 6.4*	73.3 ± 6.3*
PP, mm Hg, mean ± SD	79.5 ± 10.7	63.8 ± 11.4*	57.7 ± 9.5*	54.0 ± 8.4*

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure. *P < 0.001 *vs* baseline.

Rate of target SBP achievement

SBP reductions to less than 140 mmHg were observed after 2 weeks in 265 (43.1%) patients, after 1 month in 458 (74.5%) patients, and after 3 months in 569 (92.5%) patients. An SBP level of less than 130 mmHg was achieved after 2 weeks in 74 (12.0%) patients, after 1 month in 209 (34.0%) patients and after 3 months in 344 (55.9%) patients.

Patients aged 55–59 years old had the highest levels of target SBP level achievement after 3 months of treatment (95% achieved a target of < 140 mmHg and 61% a target of < 130 mmHg), while the lowest proportions of patients achieving the two blood pressure targets were found in those aged older than 80 years (79% and 31%, respectively).

Changes in PP levels

A significant reduction in PP levels during the treatment was also observed in the different age groups (Table 4). Mean PP reductions after 3 months of treatment were 24.0 ± 11.1, 25.6 ± 11.0, 26.4 ± 11.8, and 25.5 ± 8.4 mmHg in the 55–59, 60–69, 70–79, and 80 years and older age groups, respectively. A PP of < 60 mmHg was achieved by 82% of patients after 3 months of treatment.

Table 4
Changes in pulse pressure (PP) during the treatment in different age groups.

Age	Baseline, mean ± SD	Week 2, mean ± SD	Month 1, mean ± SD	Month 3, mean ± SD
55–59 years	75.9 ± 9.8	61.6 ± 10.4*	55.2 ± 8.8*	52.0 ± 8.1*
60–69 years	78.4 ± 10.2	62.2 ± 11.0*	56.2 ± 9.2*	52.8 ± 8.3*
70–79 years	83.1 ± 11.2	67.2 ± 11.7*	61.1 ± 9.5*	56.7 ± 8.1*
≥ 80 years	84.7 ± 9.7	69.9 ± 11.2*	61.5 ± 9.9*	59.2 ± 8.0
Note: *P < 0.001 *vs* previous visit.				

Tolerability

Indapamide/amlodipine SPC was well tolerated by patients in the ARBALET study. A total of 16 adverse events were reported in 13/2217 patients (0.59%). Serious adverse events were reported in three (0.14%) patients: one hospitalization for unstable angina, one planned surgical intervention for cataracts, and one installation of a pacemaker. Of the non-serious adverse events, the most frequent was leg edema (5 events). One serious adverse event (unstable angina) and six non-serious adverse events (4 cases of leg edema, 1 dizziness and 1 tachycardia) led to patient discontinuation from the study.

Two cases (0.32%) of treatment-related adverse events (swelling/edema of legs and feet) were reported in this post-hoc analysis. Neither event led to patient discontinuation from the study.

Discussion

According to the latest 2020 International Society of Hypertension guidelines, ISH is the most common form of essential hypertension in the young, but is also frequently found in middle-aged individuals and the elderly, in whom it reflects stiffening of the large arteries with an increase in PP [12].

Most international guidelines, including the latest 2020 Canadian guidelines [13], support a diuretic and CCB combination for the treatment of ISH. This is based on data from a number of studies in which a diuretic and CCB combination in subpopulations of patients with ISH was shown to be an effective treatment option for reducing SBP and cardiovascular events with a favorable safety profile [14–17].

Thiazide-like diuretics are generally preferred over thiazide diuretics based on duration of action data, their BP-lowering ability, and long-term cardiovascular endpoint reduction data [18]. A 2015 meta-analysis of four large outcome trials including 30,791 patients with a mean age of 64 years, found that a thiazide-like diuretic/CCB combination was associated with a 23% reduction in the risk of stroke and 17%

reduction in the risk of myocardial infarction, and a comparable effect on all-cause mortality to that of other combination strategies [19]. Based on existing evidence, the new 2020 International Society of Hypertension guidelines specifically highlight that thiazide diuretics should only be used in the situation when thiazide-like diuretics are not available. The guidelines also recommend that treatments should be evidence-based in relation to morbidity/mortality prevention, and provide a once-daily regimen that offers 24 h blood pressure control with evidence of medication benefits in the populations to which they are to be applied [12].

Both indapamide and amlodipine are supported by data in relation to this recommendation. Beyond their efficacy in reducing high blood pressure and improving target-organ damage, both agents have separately demonstrated benefits in terms of morbidity and mortality (HYVET, PATS, PROGRESS, ADVANCE, ALLHAT, ASCOT-BPLA, VALUE, ACCOMPLISH, CAMELOT, PREVENT, Syst-EUR, STOP Hypertension-2, Syst-China, trials) [14, 20–30] with a decrease in total and cardiovascular mortality, and a reduction in morbidities related to the brain, heart, and kidney, depending on the study.

A number of studies have shown that ISH is associated with a significant increase in the risk of adverse cardiovascular outcomes including CAD, cerebrovascular disease and heart failure [6, 31, 32]. A thiazide-like diuretic and a long-acting CCB is a rational combination in such patients. A meta-analysis of ELSA (European Lacidipine Study on Atherosclerosis), VALUE (The Valsartan Antihypertensive Long-Term Use Evaluation), FEVER (Felodipine Event Reduction study) and COPE (Combination Therapy for Hypertension to Prevent Cardiovascular Events) trials (n = 30791) confirmed that co-administration of a CCB and thiazide diuretic is the most effective combination for reducing the risks of stroke and myocardial infarction (RR reduction by 27% and 17%, respectively), compared with other antihypertensive therapy combinations, with a comparable effect on all-cause mortality [19].

In the present post-hoc analysis of the subgroup of patients with ISH from the ARBALET trial, the addition or replacement of existing antihypertensive therapy with a once-daily indapamide/amlodipine 1.5/5 mg or 1.5/10 mg SPC for 3 months was associated with statistically significant BP reductions ranging from – 28.9 to -32.5 mmHg compared with baseline across all age categories. Efficacy and safety of treatment in the ISH subgroup were comparable to results observed in the main ARBALET trial population [11]. Reductions in office BP levels were observed from as early as 2 weeks and continued to decrease such that mean values were in line with BP targets recommended by the 2018 ESC/ESH guidelines for the management of arterial hypertension by the end of the study. The SBP target of < 140 mmHg was met by 43.1% of patients at 2 weeks and by 92.5% at 3 months and the target of < 130 mmHg by 12.0% of patients at 2 weeks and by 55.9% at 3 months. As a result of the appointment of a fixed combination of indapamide and amlodipine, the use of different classes of antihypertensive drugs decreased during the study. The exception was beta-blockers, for which prescriptions in patients with ISH increased from 31–34% during study.

The degree of BP reduction remains the main determinant of vascular risk reduction in both young and elderly patients [33, 34]. While the highest proportion of patients achieving both the < 140 mmHg and <

130 mmHg targets at 3 months was observed in those aged 55–59 years, all age groups benefited from the replacement or addition of the SPC to their treatment plan.

ISH is not uncommon in middle-aged adults as observed in the current study where 22% of patients were less than 60 years' old. In older patients, age-related large artery stiffening becomes the most important pathophysiological determinant of ISH [35], but reduced vascular compliance and increased arterial stiffness can also be accelerated with certain conditions such as obesity and diabetes and by smoking. The ARBALET study population was typical of that found in real clinical practice and included a high proportion of patients with cardiovascular risk factors such as dyslipidemia and obesity as well as concomitant cardiovascular diseases. The high rates of SBP control in the present analysis confirm data from previous studies showing that indapamide/amlodipine may represent an effective treatment for reducing BP in a broad range of patients with ISH [36–38]. The observed results were also greater than those demonstrated with a diuretic/ARB combination in patients with ISH in a post-hoc analysis of the INCLUSIVE trial where a mean reduction of 21 mmHg was observed at 18 weeks with an SBP control rate (< 140 mmHg) of 74% [39].

Reduced nitric oxide release by the endothelium, high salt sensitivity, oxidative stress, inflammation and increased BP variability are just some of the factors that are associated with ISH [40]. All of these represent targets for thiazide-like diuretics and dihydropyridine-type CCB, and both types of agent are among first-line treatments for hypertension and are the preferred first-line agents for ISH [13, 40]. In addition to lowering BP, amlodipine has antioxidant and anti-inflammatory properties [41, 42], and enhances NO production by the endothelium [43]. Indapamide also has a number of benefits that are independent of its diuretic effects including CCB-like vasodilatory effects [44], vasodilatory effects due to stimulation of prostaglandin I_2 [45], and antioxidative effects [46]. Both large artery stiffening and sodium sensitivity increase with age, so that drugs targeting both risk factors are likely to be of benefit in patients with ISH.

A comparison of indapamide SR, candesartan, amlodipine and placebo in a population with ISH showed that changes in SBP and PP were similar with the three treatments, but only indapamide did not change DBP and thus reduced PP significantly relative to placebo [47]. Furthermore, an analysis of the ambulatory BP monitoring data from this study showed that 3-month indapamide SR or amlodipine treatment was associated with a significant reduction in BP variability, increased levels of which are associated with arterial stiffening [48].

The effect of indapamide/amlodipine treatment on SBP has been demonstrated in two single-arm, open-label studies. In the NATIVE study (mean age of total study population 51 years), indapamide SR was added to background antihypertensive therapy [36]. In the subgroup of patients who received indapamide and amlodipine, SBP was decreased by 33 mmHg compared with baseline. In the EFFICIENT study (mean age 52 years) the single pill combination of indapamide/amlodipine at a dose of 1.5 mg/5 mg for 45 days resulted in a decrease in SBP of 29 mmHg compared with baseline [37].

The populations in the above trials were middle-aged, but the benefits of treating ISH in the elderly are also well established as first demonstrated 30 years ago in SHEP (mean age – 72 years), where active treatment with a diuretic with or without a beta-blocker reduced mean SBP by 12 mmHg more than placebo [49]. Those randomized to diuretic treatment had marked reductions in the rates of myocardial infarction (– 27%), heart failure (– 55%), and stroke (– 37%). This was followed by the Syst-EUR trial where antihypertensive drug treatment with a CCB plus ACE-inhibitor or diuretic reduced SBP by 10 mmHg compared with placebo with reductions in cardiovascular outcomes similar to those in SHEP [28].

The BP-lowering efficacy of an indapamide SR/amlodipine combination in patients with hypertension and diabetes was examined in a retrospective post-hoc analysis of the NESTOR trial [38]. A total of 107 patients aged 65 years and older, half of whom had ISH, received dual therapy with either indapamide SR/amlodipine or enalapril/amlodipine. At 52 weeks, indapamide SR/amlodipine resulted in superior SBP reduction to the enalapril/amlodipine combination – 29.6 vs -22.4 mmHg, respectively, with an equivalent tolerability [38].

Older individuals comprise a large proportion of the ISH patients and with an aging population this is only expected to increase. The results from the ARBALET ISH cohort are in line with results of studies conducted in older individuals with ISH. In the SHEP study (mean age – 72 years), the mean reduction of SBP was 26 mmHg on therapy with a diuretic or beta-blocker [49] compared with – 32.5 mmHg in the ARBALET ISH subgroup aged 70–79 years. Another study in elderly hypertensive patients, around a quarter of whom had ISH, compared the efficacy of indapamide sustained-release 1.5 mg in reducing BP versus amlodipine 5 mg and hydrochlorothiazide 25 mg [50]. In the ISH subgroup, indapamide 1.5 mg tended to have greater efficacy than hydrochlorothiazide at reducing SBP (-24.7 versus – 18.5 mmHg, respectively; equivalence $P = 0.117$), and similar results to amlodipine (-23 mmHg, equivalence $P < 0.001$) [50]. In the Medical Research Council study, patients aged 65–74 years with systolic hypertension, with or without diastolic hypertension, were randomized to diuretic, beta blocker, or placebo. SBP and DBP decreased in all groups, with the greatest systolic fall seen in the diuretic group in the first 3 months [51]. Taking into account the reduction in renin-angiotensin-aldosterone system (RAAS) activity with age and the prevalence of sodium-volume-dependent forms of hypertension in elderly patients, the use of an amlodipine/thiazide-like diuretic FDC represents a rationale option when choosing an antihypertensive therapy regimen in older patients.

SBP and PP are closely related and elevated SBP and a wide PP are recognized as independent cardiovascular risk factors. In the ARBALET population with ISH, the addition of indapamide/amlodipine was associated with a significant reduction in PP such that it was reduced to below guideline recommended target (< 60 mmHg) in all age groups at 3 months. Treatment of ISH may further increase PP if DBP is lowered to a greater extent than SBP. However, this was not the case in the current study, where mean DBP reductions over 3 months were in the region of 6 mmHg compared with a mean SBP reduction of 32 mmHg.

The population of patients included in the present analysis of the ARBALET study comprised individuals aged 55 years and older with ISH, almost two thirds of whom were women, with a high prevalence of cardiovascular risk factors. The high rates of SBP control confirm data from previous studies showing that indapamide/amlodipine SPC as either a replacement or addition to existing therapy, or as preliminary therapy in treatment naïve patients, may represent an effective means of reducing SBP in a broad range of patients of all ages, with common cardiovascular comorbidities.

Indapamide/amlodipine was well tolerated in the ISH subgroup with similar rates of adverse events to patients in the main ARBALET study. The adverse event profile was in line with the proven tolerability of indapamide and amlodipine, both alone and in combination.

Study limitations

This was a post-hoc analysis of an observational open-label study without a control group and as such the results require confirmation in further clinical trials. The SPC was added to existing antihypertensive therapy in 80 (13%) of patients and therefore the treatment effect cannot be attributed to the SPC alone. Finally, this post-hoc analysis included only office BP measurements while the main ARBALET study included both office and ambulatory BP measurements.

Conclusion

In this post-hoc analysis of patients from the ARBALET trial with ISH, the single-pill combination of indapamide/amlodipine was associated with significant reductions in SBP in a broad range of patients of all ages typically found in clinical practice. Treatment was well tolerated and effective either when added to or replacing existing antihypertensive treatment as well as in treatment-naïve patients and was associated with high rates of target SBP and PP achievement.

List Of Abbreviations

ACE - angiotensin-converting enzyme

BP - blood pressure

CHF - chronic heart failure

CVD - cardiovascular disease

DBP - diastolic blood pressure

HR - heart rate

HT - hypertension

ISH - isolated systolic hypertension

PP - pulse pressure

SBP - systolic blood pressure

Declarations

Author contributions

All authors contributed equally to the design, data analysis and preparation of this manuscript. All authors read and approved the final manuscript.

Disclosures

Prof Kobalava has received fees from Servier as a speaker and an investigator. Other authors declare the absence of a potential conflict to disclose in relation to this article.

Compliance with ethics guidelines

All diagnostic procedures were performed based on written informed patient consent. The study was conducted in accordance with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. The study protocol was approved by the ethical committees in all participating clinical sites.

Funding

Sponsorship for this study was provided by Servier, Moscow, Russian Federation.

Acknowledgments

Editorial assistance was provided by Jenny Grice, BSc and funded by Servier, France.

Article processing charges were funded by Servier, France.

References

1. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–3104.
2. Kobalava ZD, Kotovskaya YV, Aseeva OA, et al. Clinical and demographic characteristics of different variants of hypertension in elderly patients (according to the results of the Russian scientific and practical program ARGUS). Terapevticheskiy Arkhiv. 2002;74(2):47–51. [*in Russian*]
3. Vishnevsky AG, Andreev EM, Timonin SA. Mortality from circulatory system diseases and life expectancy in Russia. Demograficheskoye Obozreniye. 2016;3(1):6–34. [*in Russian*]
4. Kobalava JD, Shavarova EK, Khomova IA, et al. Fixed-dose combination of amlodipine and indapamide-retard in the treatment of uncontrolled hypertension in people over 55 years of age. Arterial'naya Gipertenziya. 2018;24(5):586–594. [*in Russian*].

5. Liu X, Rodriguez CJ, Wang K. Prevalence and trends of isolated systolic hypertension among untreated adults in the United States. J Am Soc Hypertens. 2015;9(3):197-205.
6. O'Donnell CJ, Ridker PM, Glynn RJ, et al. Hypertension and borderline isolated systolic hypertension increase risks of cardiovascular disease and mortality in male physicians. Circulation. 1997;95(5):1132-1137.
7. Nilsson PM, Olsen MH, Laurent S (eds). *Early vascular aging (EVA): New directions in cardiovascular protection.* Academic Press, 2015. https://doi.org/10.1016/C2013-0-19168-4.
8. Franklin SS, Pio JR, Wong ND, et al. Predictors of new-onset diastolic and systolic hypertension: the Framingham Heart Study. Circulation. 2005;111(9):1121–1127.
9. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC 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). Eur. Heart J. 2013;34(28):2159–2219.
10. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. JAMA. 2010;303(20):2043–2050.
11. Kobalava ZD, Tolkacheva VV, Bagmanova NC, Khasanova ER. Efficacy and tolerability of Arifam in patients with hypertension aged over 55 years: main results of the ARBALET observational program. Rossiyskiy Kardiologicheskiy Zhurnal. 2018;(12):64–74. [*in Russian*].
12. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020;75(6):1334-1357.
13. Rabi DM, McBrien KA, Sapir-Pichhadze R, et al. Hypertension Canada's 2020 comprehensive guidelines for the prevention, diagnosis, risk assessment, and treatment of hypertension in adults and children. Can J Cardiol. 2020;36(5):596-624.
14. Julius S, Kjeldsen SE, Weber M, et al; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363:2022–2031.
15. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359(23):2417–2428.
16. Lu F, Zhao Y, Liu Z, et al. A 48-week study of amlodipine plus amiloride/hydrochlorothiazide vs. amlodipine plus telmisartan in the treatment of hypertension. Int J Clin Pract. 2012;66(8):792-799.
17. Matsuzaki M, Ogihara T, Umemoto S, et al; Combination Therapy of Hypertension to Prevent Cardiovascular Events Trial Group. Prevention of cardiovascular events with calcium channel blocker-based combination therapies in patients with hypertension: a randomized controlled trial. J Hypertens. 2011;29(8):1649-1659.
18. Burnier M. Treatment of hypertension in the elderly in 2017/2018 - what's new? Expert Opin Pharmacother. 2019;20(15):1869-1877.
19. Rimoldi SF, Messerli FH, Chavez P, et al. Efficacy and safety of calcium channel blocker/diuretics combination therapy in hypertensive patients: a meta-analysis. J Clin Hypertens (Greenwich).

2015;17(3):193–199.

20. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358(18):1887–1898.
21. PATS Collaborating Group. Post-stroke antihypertensive treatment study. A preliminary result. Chin Med J (Engl*)*. 1995;108(9):710-717.
22. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack [published correction appears in Lancet 2001 Nov 3;358(9292):1556] [published correction appears in Lancet 2002 Jun 15;359(9323):2120]. Lancet. 2001;358(9287):1033-1041.
23. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981–2997.
24. Dahlöf B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366:895–906.
25. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359(23):2417-2428.
26. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004;292(18):2217-2225.
27. Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events. PREVENT Investigators. Circulation. 2000;102:1503–1510.
28. Staessen JA, Fagard R, Thijs L, 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(9080):757–764.
29. Hansson L, Lindholm LH, Ekbom T, 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(9192):1751–1756.
30. Liu L, Wang J, Gong L, et al. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. J Hypertens. 1998;16(12):1823–1829.
31. Ekundayo OJ, Allman RM, Sanders PW, et al. Isolated systolic hypertension and incident heart failure in older adults: a propensity-matched study. Hypertension. 2009;53(3):458-465.
32. Li Y, Wei FF, Thijs L, et al. Ambulatory hypertension subtypes and 24-hour systolic and diastolic blood pressure as distinct outcome predictors in 8341 untreated people recruited from 12 populations. Circulation. 2014;130(6):466-474.

33. Blood Pressure Lowering Treatment Trialists' Collaboration, Turnbull F, Neal B, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ. 2008;336(7653):1121–1123.
34. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
35. Laurent S, Cockcroft J, Van Bortel L, et al; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: ethodological issues and clinical applications. Eur Heart J. 2006;27:2588–2605.
36. Akram J, Sheikh UE, Mahmood M, Donnelly R. Antihypertensive efficacy of indapamide SR in hypertensive patients uncontrolled with a background therapy: the NATIVE study. Curr Med Res Opin. 2007;23(12):2929-2936.
37. Jadhav U, Hiremath J, Namjoshi DJ, et al. Blood pressure control with a single-pill combination of indapamide sustained-release and amlodipine in patients with hypertension: the EFFICIENT study. PLoS One. 2014;9(4):e92955.
38. Hanon O, Caillard L, Chaussade E, Hernandorena I, Boully C. Blood pressure-lowering efficacy of indapamide SR/amlodipine combination in older patients with hypertension: A post hoc analysis of the NESTOR trial (Natrilix SR vs Enalapril in Hypertensive Type 2 Diabetics With Microalbuminuria). J Clin Hypertens (Greenwich). 2017;19(10):965-972.
39. Chrysant SG, Ferdinand KC. Irbesartan/hydrochlorothiazide for the treatment of isolated systolic hypertension: a subgroup analysis of the INCLUSIVE trial. J Natl Med Assoc. 2009;101:300-307.
40. Bavishi C, Goel S, Messerli FH. Isolated systolic hypertension: an update after SPRINT. Am J Med. 2016;129:1251-1258.
41. Celık T, Balta S, Karaman M, et al. Endocan, a novel marker of endothelial dysfunction in patients with essential hypertension: comparative effects of amlodipine and valsartan. Blood Press. 2015;24:55–60.
42. Kim HJ, Han SJ, Kim DJ, et al. Effects of valsartan and amlodipine on oxidative stress in type 2 diabetic patients with hypertension: a randomized, multicenter study. Korean J Intern Med. 2017;32:497–504.
43. Berkels R, Taubert D, Bartels H, Breitenbach T, Klaus W, Roesen R. Amlodipine increases endothelial nitric oxide by dual mechanisms. Pharmacology. 2004;70:39–45.
44. Pickkers P, Hughes AD, Russel FG, Thien T, Smits P. Thiazide-induced vasodilation in humans is mediated by potassium channel activation. Hypertension. 1998;32(6):1071-1076.
45. Delbarre B, Delbarre G, Ferger A. [Role of prostaglandins in the mechanism of action of indapamide]. Arch Mal Coeur Vaiss. 1990;83(8):1209-1212.
46. Vergely C, Walker MK, Zeller M, et al. Antioxidant properties of indapamide, 5-OH indapamide and hydrochlorothiazide evaluated by oxygen-radical absorbing capacity and electron paramagnetic resonance. Mol Cell Biochem. 1998;178(1-2):151-155.

47. London G, Schmieder R, Calvo C, Asmar R. Indapamide SR versus candesartan and amlodipine in hypertension: the X-CELLENT Study. Am J Hypertens. 2006;19(1):113-121.
48. Zhou TL, Henry RM, Stehouwer CD, van Sloten TT, Reesink KD, Kroon AA. Blood pressure variability, arterial stiffness, and arterial remodeling. Hypertension. 2018;72(4):1002-1010.
49. 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(24):3255-3264.
50. Emeriau JP, Knauf H, Pujadas JO, et al. A comparison of indapamide SR 1.5 mg with both amlodipine 5 mg and hydrochlorothiazide 25 mg in elderly hypertensive patients: a randomized double-blind controlled study. J Hypertens. 2001;19(2):343-350.
51. MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. BMJ. 1992;304:405-412.