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Blood Pressure Control with a Single-Pill Combination of Indapamide Sustained-Release and Amlodipine in Patients with Hypertension: The EFFICIENT Study

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Abstract

Objective: Despite antihypertensive treatment, most hypertensive patients still have high blood pressure (BP), notably high systolic blood pressure (SBP). The EFFICIENT study examines the efficacy and acceptability of a single-pill combination of sustained-release (SR) indapamide, a thiazide-like diuretic, and amlodipine, a calcium channel blocker (CCB), in the management of hypertension.

Methods: Patients who were previously uncontrolled on CCB monotherapy (BP≥140/90 mm Hg) or were previously untreated with grade 2 or 3 essential hypertension (BP≥160/100 mm Hg) received a single-pill combination tablet containing indapamide SR 1.5 mg and amlodipine 5 mg daily for 45 days, in this multicenter prospective phase 4 study. The primary outcome was mean change in BP from baseline; percentage of patients achieving BP control (BP<140/90 mm Hg) was a secondary endpoint. SBP reduction (ΔSBP) versus diastolic BP reduction (ΔDBP) was evaluated (ΔSBP/ΔDBP) from baseline to day 45. Safety and tolerability were also assessed.

Results: Mean baseline BP of 196 patients (mean age 52.3 years) was 160.2/97.9 mm Hg. After 45 days, mean SBP decreased by 28.5 mm Hg (95% CI, 26.4 to 30.6), while diastolic BP decreased by 15.6 mm Hg (95% CI, 14.5 to 16.7). BP control (<140/90 mm Hg) was achieved in 85% patients. ΔSBP/ΔDBP was 1.82 in the overall population. Few patients (n = 3 [2%]) reported side effects, and most (n = 194 [99%]) adhered to treatment.

Conclusion: In patients who were previously uncontrolled on CCB monotherapy or untreated with grade 2 or 3 hypertension, single-pill combination indapamide SR/amlodipine reduced BP effectively—especially SBP— over 45 days, and was safe and well tolerated.

Trial Registration: Clinical Trial Registry – India CTRI/2010/091/000114

Introduction

Elevated blood pressure (BP) is one of the most important risk factors for cardiovascular mortality [1], and BP lowering is associated with reductions in cardiovascular and renal outcomes [2,3]. BP lowering that leads to BP control, however, is achieved in less than a third of hypertensive patients [4]. Systolic blood pressure (SBP), in particular, is difficult to control in clinical practice [5]. SBP, which is a better predictor of cardiovascular risk than DBP, increases linearly from 30 years, while diastolic blood pressure (DBP) decreases from 50 years [6].

Initiating treatment with a single-pill combination of two antihypertensive agents has been shown to be significantly more effective and faster at controlling BP than using the same two agents in a sequential drug titration strategy [7,8]. International guidelines on hypertension recommend initiation of treatment with a single-pill combination in hypertensive patients with multiple cardiovascular risk factors, evidence of organ damage,

or grade 2 or 3 hypertension [9–11]. Antihypertensive treatment compliance is also significantly better with a single-pill combination than with a combination's components given separately [12]. In consequence, initiation of antihypertensive treatment with single-pill combinations is becoming more common.

The 2013 European guidelines on hypertension management give calcium channel blocker (CCB)/diuretic single-pill combinations preferred status based on promising results from randomized controlled trials, including VALUE (Valsartan Antihypertensive Long-term Use Evaluation) and FEVER (Felodipine EVEnt Reduction) [13–15]. This combination is a good option in hypertensive patients with low renin levels who are inadequately controlled by a renin-angiotensin-aldosterone system (RAAS) inhibitor [16]. The prevalence of isolated systolic hypertension is likely to increase as the proportion of elderly patients in populations around the world increases, so the need for therapeutic answers to elevated SBP is growing. Diuretics and CCBs have been found to be the most effective antihypertensive classes for SBP reduction, and the best agents in these classes in one meta-analysis of 10 818 patients were indapamide SR and amlodipine [17].

The first single-pill representative of this CCB/diuretic combination recently became available in Europe. Its individual components—indapamide sustained-release 1.5 mg (SR), a thiazide-like diuretic, and amlodipine 5 or 10 mg, a CCB—have been shown to reduce hypertension [17,18] and cardiovascular risk [2,19] in randomized controlled trials. In a recent meta-analysis of 160 000 hypertensive subjects, amlodipine and indapamide were two of the three antihypertensive agents to significantly reduce mortality [20], indicating the potential of this particular combination. To determine its clinical relevance, we describe a multicenter, prospective, phase 4 study, EFFICIENT (EFfects of a FIxed Combination of Indapamide sustained-release with amlodipine on blood prEssure iN hyperTension), which examines the effects of single-pill combination indapamide SR/amlodipine 1.5/5 mg on BP reduction, BP control, and adverse events in a primary healthcare setting [21].

Methods

The protocol for this trial and supporting TREND checklist are available as supporting information; see **Protocol S1** and **Checklist S1**.

Ethics statement

The study protocol was approved by the ethics committees of each participating center. Ethics committee approval was therefore obtained from the following organizations: Ethics Committee, MGM New Bombay Hospital, Mumbai (date of approval, 28 January 2010), Clinical Ethics Forum, Mumbai (16 February 2010), Ethics Committee, Faculty of Medical Sciences, Banaras Hindu University, Varanasi (3 March 2010), Clinical Ethics Forum, Mumbai (16 February 2010), Bangalore Central Ethics Committee, Bangalore (27 January 2010), Institutional Ethics Committee, Deccan College of Medical Sciences & Allied Hospitals, Hyderabad (12 January 2010), and Ethics Committee, Poona Hospital & Research Centre, Pune (3 April 2010). The study, which is publicly registered (CTRI No.: 2010/091/000114), complies with the Guidelines for Clinical Trials on Pharmaceutical Products in India and also with the Good Clinical Practice Guidelines issued by the Central Drugs Standard Control Organisation of the Indian Ministry of Health. The study was performed in accordance with the principles stated in the Declaration of Helsinki, and all patients gave written informed consent.

Study design

This 45-days multicenter, open, noncomparative, prospective phase 4 study in an urban primary care setting included consecutive adult outpatients of either sex who were either uncontrolled on CCB monotherapy (≥140/90 mm Hg, or both) or newly diagnosed with grade 2 (SBP 160–179 mm Hg or DBP 100–109 mm Hg) or grade 3 essential hypertension (SBP≥180 or DBP≥100 mm Hg). Patients with a history of hypersensitivity to indapamide or amlodipine, or contraindication to thiazide-like diuretics or CCBs, were excluded from the study. Other exclusion criteria included a recent (within 3 months) history of myocardial infarction or cerebrovascular event; history of heart failure; uncontrolled arrhythmia; uncontrolled diabetes; severe renal dysfunction (estimated glomerular filtration rate [eGFR] <30 mL/min); serious liver disorders; pregnancy; or lactation.

Seven physicians with experience in hypertension management, and adequate clinical and laboratory facilities, recruited hypertensive patients eligible to receive the study medication between April 29 and August 27, 2010, and agreed to implement the study protocol.

Patients previously uncontrolled on CCB monotherapy stopped their previous CCB. All patients received one tablet of single-pill combination indapamide SR/amlodipine 1.5/5 mg in the morning for the next 45 days. Treatment of associated disease was allowed at the discretion of the physician, but concurrent antihypertensive medication was forbidden. Patients were followed up and reassessed after 15, 30, and 45 days, up to the conclusion of the study on October 11, 2010. Laboratory investigations, which included hematology, biochemistry, urinalysis, and electrocardiography, were carried out at the preselection visit and last study visit. At each follow-up visit, BP was measured by mercury sphygmomanometer in the morning, with the patient sitting. The average of 3 readings was recorded. To compare the relative antihypertensive efficacy of indapamide SR/amlodipine in reducing SBP (ΔSBP) versus DBP (ΔDBP), a ΔSBP/ΔDBP ratio from baseline to day 45 was calculated. Patients were also asked open-ended questions about side effects experienced since the previous visit.

The primary outcome was mean BP change from baseline to end. The number of patients achieving BP control (<140/90 mm Hg) was a secondary outcome. Safety and tolerability were also evaluated via reporting of side effects, including pedal edema, and monitoring of laboratory parameters.

Statistical methods

Baseline characteristics are summarized as number of patients and percentage (%) for categorical variables and mean±standard deviation for continuous variables. The analysis was performed on an intention-to-treat basis. The underlying assumption of the statistical analysis was that all variables had a normal probability distribution. Values for baseline BP, end BP, and BP reduction from baseline to days 15, 30, and 45 are presented as means (mm Hg) and corresponding 95% confidence intervals (CI) using a paired t-test. These mean values were used to show the systolic and diastolic BP response to indapamide SR/amlodipine for all hypertensive patients, those previously untreated with grade 2 or grade 3 hypertension, those uncontrolled BP on CCB monotherapy, and diabetes. BP control (<140/90 mm Hg) was summarized as numbers of patients and percentages (%). A paired t-test was used to assess changes in laboratory parameters from baseline to 45 days for significance. Significance was defined as a two-tailed p

value<0.05. Data were analyzed using the statistics program SPSS version 11.

Results

Baseline characteristics are presented in **Table 1**. Mean age of the 196 patients was 52.3 years, just over half (51%) were female, and nearly two-thirds (65%) had grade 2 (n = 115 [59%]) or 3 (n = 12 [6%]) hypertension. Baseline BP in the overall population was 160.2±15.1/97.9±6.8 mm Hg. No patients had severe renal dysfunction (eGFR <30 mL/min). Previously untreated patients constituted over half (n = 108 [55%]) the population, and under half (n = 88 [45%]) were uncontrolled on CCB monotherapy. Thirty-one patients (16%) had diabetes. Over the course of the study, 18 (9%) patients withdrew (lack of efficacy in 1 [<1%],

Table 1. Baseline characteristics of hypertensive patients eligible to receive single-pill combination indapamide SR/amlodipine 1.5 mg/5 mg.

	N = 196
Demographic characteristics	
Age (years)	52.3±11.4
Sex (female)	99 (51%)
Current smoker	11 (6%)
Body mass index (kg/m^2)	26.1±4.6
Cardiovascular risk	
Systolic blood pressure (mm Hg)	160.2±15.1
Diastolic blood pressure (mm Hg)	97.9±6.8
Coronary artery disease	5 (3%)
TC/HDL ratio	4.2±0.82
Left ventricular hypertrophy	3 (2%)
Diabetes	31 (16%)
Medical history	
Grade 1 hypertension	69 (35%)
Grade 2 hypertension	115 (59%)
Grade 3 hypertension	12 (6%)
Prior antihypertensive treatment	
CCB monotherapy	88 (45%)
Untreated	108 (55%)
Laboratory parameters	
Fasting plasma glucose (mg/dL)	100.8±27.2
Total cholesterol (mg/dL)	180.5±32.0
LDL cholesterol (mg/dL)	105.9±32.3
HDL cholesterol (mg/dL)	43.7±12.1
Triglycerides (mg/dL)	133.3±61.3
Serum sodium (mEq/L)	139.6±10.2
Serum potassium (mEq/L)	4.2±0.5
Serum creatinine (mg/dL)	0.9±0.2
eGFR* (mL/min)	87.8±30.6

Values are means±standard deviation. All other values are numbers and percentages. CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SR, sustained-release; TC, total cholesterol.
*calculated using the 4-variable MDRD formula.
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dizziness in 2 [1%], other reasons in 2 [1%], and 13 [7%] lost to follow-up) (**Figure 1**).

Treatment with single-pill combination indapamide SR/amlodipine reduced overall mean BP by 16.7/10.9 mm Hg after 15 days and by 28.5/15.6 mm Hg at 45 days (**Figure 2 and Table 2**). In patients previously uncontrolled on CCB monotherapy (most commonly amlodipine 5 mg), SBP and DBP fell by 22.0 and 13.1 mm Hg after 45 days. Over the same period, SBP and DBP fell by 33.1 and 18.4 mm Hg in patients with grade 2 hypertension, and by 51.2 and 20.3 mm Hg in patients with grade 3 hypertension. In the overall population, most patients (n = 166 [85%]) achieved BP control (<140/90 mm Hg) after 45 days' treatment (**Figure 3**). By day 45, the percentage of controlled hypertensive patients was 82% (n = 72) in patients previously uncontrolled on CCB monotherapy and 87% (n = 94) in previously untreated patients. In the overall population, ΔSBP/ΔDBP was 1.83 from baseline to day 45. The corresponding ΔSBP/ΔDBP ratios in grade 2 and grade 3 hypertensive patients were 1.80 and 2.52 (**Figure 2**).

Adverse events were reported by 3 (2%) patients. Of these, 2 (1%) experienced dizziness leading to withdrawal, and 1 (<1%) complained of weakness (but completed the study). No other side effects were reported, in particular pedal edema. After 45 days, there were no clinically relevant changes in laboratory parameters versus baseline: plasma fasting glucose, −2.8 mg/dL (p = 0.096); serum sodium, −0.08 mEq/L (p = 0.94); serum potassium, −0.08 mEq/L (p = 0.68); total cholesterol, +1.2 mg/dL (p = 0.58); high-density lipoprotein cholesterol, +0.39 mg/dL (p = 0.74); low-density lipoprotein cholesterol, +1.6 mg/dL (p = 0.43); triglycerides, +7.3 mg/dL (p = 0.03); and no change in serum creatinine (p = 0.89). Most patients (n = 194 [99%]) adhered to treatment.

Discussion

Treatment with once-daily indapamide SR/amlodipine 1.5/5 mg led to a mean reduction in BP of 28.5/15.6 mm Hg after 45 days and controlled hypertension (BP<140/90 mm Hg) in 85% of the overall population. Response to treatment was similar, regardless of whether patients were previously uncontrolled on CCB monotherapy, untreated, or had a history of diabetes. Treatment was well tolerated, with few patients reporting side effects or discontinuing treatment, and adherence was satisfactory. There were no new cases of pedal edema or hypokalemia. No clinically relevant changes in laboratory parameters were reported.

BP control in our study was initially better in patients uncontrolled on CCB monotherapy than in untreated patients, but the rate of BP control was more rapid in untreated patients so by the end of the study, this situation had reversed. In clinical practice, uncontrolled SBP is largely responsible for the low BP control rate observed [6]. High SBP is more difficult to manage and requires more drug therapy to control than high DBP. The 2013 European guidelines on hypertension management acknowledge the usefulness of both diuretics and CCBs in isolated systolic hypertension by listing them as preferred antihypertensive agents in this condition [13]. Systolic hypertension has also been observed in middle-aged hypertensive patients, in whom it is associated with an increased risk of cardiovascular mortality [22]. Both indapamide SR and amlodipine have been shown to be particularly effective at reducing SBP [17]. The magnitude of the blood pressure reduction seen with indapamide SR/amlodipine in our study was in line with what was expected, considering the two agents separately [17].
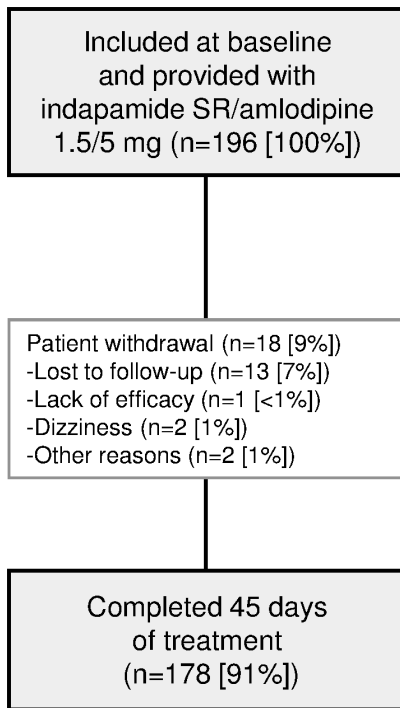
Figure 1. Study flowchart.
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SBP reduction with indapamide SR/amlodipine compared favorably with that of other antihypertensive single-pill combinations assessed for efficacy and acceptability. Single-pill combinations containing a diuretic and RAAS blocker have ΔSBP/ΔDBP ratios that ranged from 1.34 ($-20.3/-15.2$ mm Hg with valsartan 160 mg/HCTZ 12.5 mg) to 1.69 ($-21.1/-12.5$ mm Hg with valsartan 320 mg/HCTZ 25 mg) [23,24], compared with 1.83 ($-28.5/-15.6$ mm Hg) with indapamide SR 1.5 mg/amlodipine 5 mg. In patients with the severe hypertension (grade 3), the ΔSBP/ΔDBP ratio after 6 weeks with losartan 50 mg/hydrochlorothiazide 12.5 mg was 1.41 ($-25.1/-17.8$ mm Hg) [23], and 1.37 ($-33.2/-24.2$ mm Hg) with valsartan 320 mg mg/HCTZ 25 mg [25], compared with 2.52 ($-51.2/20.3$ mm Hg) with indapamide SR 1.5 mg/amlodipine 5 mg in our study. Comparison with antihypertensive monotherapy showed that BP reduction over 8 to 12 weeks with diuretics was greater than that of other antihypertensive classes: $-19.2/-11.1$ mm Hg versus $-16.4/-11.4$ mm Hg with CCBs, $-15.6/-10.8$ mm Hg with ACE inhibitors, $-14.8/-11.4$ mm Hg with beta-blockers, $-13.5/-11.3$ with direct renin inhibitor, and $-13.2/-10.3$ mm Hg with ARBs [17]. In this meta-analysis, indapamide SR 1.5 mg and amlodipine 5 mg were the best agents in their classes, reducing BP by 22.2/11.7 mm Hg (n = 265) and 19.9/11.5 mm Hg (n = 316), respectively. Although frequently still used in antihypertensive combinations, thiazide diuretics, like HCTZ, are not favored by National Institute of Health and Clinical Excellence hypertension guidelines [26]. These guidelines recommend the agent used in our study, indapamide SR, on the basis of evidence from large outcome trials and indapamide's neutral electrolytic and metabolic effects.

Indapamide SR directly lowers peripheral resistance and has a direct vasorelaxant effect on blood vessels [27,28], which complements the vasodilation produced by amlodipine and enhances overall BP reduction [29,30]. Both drugs control BP over 24 hours [28,31] and have been shown to reduce SBP
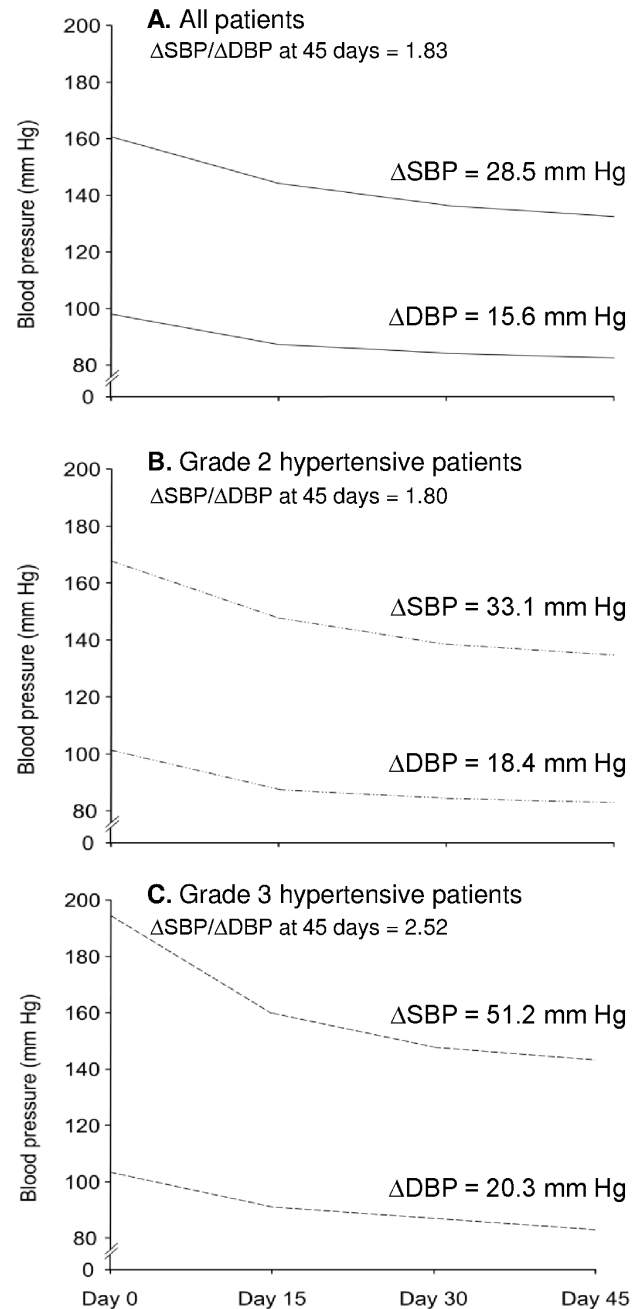

Figure 2. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) response to single-pill indapamide sustained-release/amlodipine in all hypertensive patients (panel A), patients with grade 2 hypertension (panel B), and patients with grade 3 hypertension (panel C) over 45 days. ΔSBP and ΔDBP values are at 45 days.
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variability [18]. Diuretic/CCB combinations have also been shown to successfully reduce outcomes in patients with hypertension [14,15,32]. For instance, the incidence of fatal and nonfatal myocardial infarction in VALUE was 19% less with an amlodipine/diuretic regimen than an ARB/diuretic regimen (4.1% vs 4.8%; hazard ratio, 1.19; 95% CI, 1.02 to 1.38; p = 0.02) [15]. Our adherence results corroborate previous findings that fixed-dose combination therapy in hypertension is associated with greater adherence to prescribed antihypertensive regimens [33].

Table 2. Baseline and end blood pressure, and blood pressure reduction from baseline in different groups of hypertensive patients.

Blood pressure	SBP (mm Hg)	DBP (mm Hg)
All patients		
Baseline	160.2±15.1	97.9±6.8
End	132.2±9.5	82.4±4.7
Reduction at 15 days	16.7 (14.5 to 18.9)	10.9 (9.7 to 12.1)
Reduction at 30 days	24.3 (22.1 to 26.5)	13.9 (12.7 to 15.1)
Reduction at 45 days	28.5 (26.4 to 30.6)	15.6 (14.5 to 16.7)
Patients previously uncontrolled on CCB monotherapy		
Baseline	153.1±16.2	99.9±6.4
End	130.4±9.5	82.1±5.1
Reduction at 15 days	9.9 (6.6 to 13.2)	7.6 (6.0 to 9.2)
Reduction at 30 days	18.0 (14.9 to 21.1)	10.7 (8.9 to 12.5)
Reduction at 45 days	22.0 (19.3 to 24.7)	13.1 (11.3 to 14.9)
Previously untreated patients		
Baseline	167.3±11.2	101.3±6.0
End	133.6±9.3	82.6±4.4
Reduction at 15 days	22.0 (19.5 to 24.5)	13.5 (12.0 to 15.0)
Reduction at 30 days	29.3 (26.7 to 31.9)	16.4 (14.9 to 17.9)
Reduction at 45 days	33.6 (30.0 to 36.2)	17.6 (16.3 to 18.9)
Patients with grade 2 hypertension		
Baseline	167.6±10.6	100.8±5.0
End	133.2±9.4	82.7±4.1
Reduction at 15 days	20.6 (18.3 to 22.9)	13.6 (12.1 to 15.1)
Reduction at 30 days	29.4 (26.9 to 31.9)	17.0 (15.6 to 18.5)
Reduction at 45 days	33.1 (30.7 to 35.4)	18.4 (17.0 to 19.7)
Patients with grade 3 hypertension		
Baseline	194.3±6.7	102.8±8.7
End	143.2±7.5	81.8±5.7
Reduction at 15 days	34.9 (26.4 to 43.5)	12.2 (6.2 to 18.1)
Reduction at 30 days	47.1 (39.5 to 54.7)	16.3 (11.9 to 20.8)
Reduction at 45 days	51.2 (45.1 to 57.2)	20.3 (13.7 to 26.8)
Diabetic patients		
Baseline	163.5±19.7	96.7±8.7
End	132.1±10.5	82.5±5.3
Reduction at 15 days	11.9 (2.1 to 21.7)	9.8 (6.1 to 13.5)
Reduction at 30 days	24.8 (17.5 to 32.1)	11.0 (7.1 to 14.9)
Reduction at 45 days	31.4 (25.3 to 37.5)	14.2 (10.7 to 17.7)

Values are presented as means and corresponding 95% confidence intervals or standard deviation. CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.
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The lack of new cases of pedal edema in our study might be explained by indapamide SR [27]. Postcapillary venous relaxation, the result of an indapamide SR-induced decrease in sensitivity of the vasculature to circulating catecholamines, may explain the reduced risk of edema [34]. Furthermore, low-dose CCB, eg, amlodipine 5 mg, has also been shown to be associated with a lower incidence of peripheral edema than high-dose CCB, eg, amlodipine 10 mg [35].
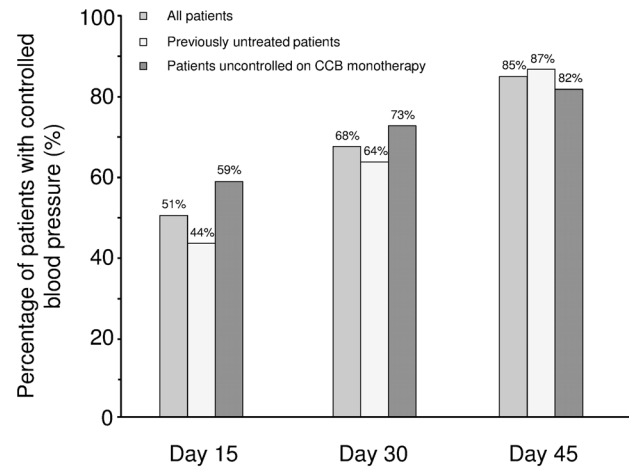

Figure 3. Blood pressure control* with single-pill indapamide sustained-release/amlodipine in hypertensive patients previously uncontrolled on CCB monotherapy and previously untreated hypertensive patients. *systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg, or both. CCB, calcium channel blocker.
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This study had the typical limitations associated with single-arm, open-label studies. The antihypertensive effect of the single-pill combination was not compared with another similar formulation using a randomized protocol. Further results (adjusted for confounding factors) from randomized controlled trials comparing indapamide SR/amlodipine with other treatment options would be useful. Other limitations were a lack of generalizability (due to the observational nature of the study) and possible regression to the mean. We cannot exclude an effect of withdrawals or loss to follow-up on our results (selection bias). Nevertheless, patients received treatment under controlled conditions, and the findings indicate the value of this antihypertensive single-pill combination in clinical practice. Our BP target of <140/90 mm Hg is slightly different from current ESH/ESC guidelines for hypertensive patients with diabetes mellitus, which propose a target of <140/85 mm Hg [13]. However, the optimal BP target for this group of patients is a subject of debate, and our target of <140/90 mm Hg is generally in line with international guidelines [36]. Our definition of severe renal dysfunction does not account for the latest KDIGO (Kidney Disease: Improving Global Outcomes) guidelines [37]. Long-term benefit was not assessed, but the efficacy and safety of both indapamide SR and amlodipine has been determined in international randomized controlled trials [2,38]. These international trials mitigate the limitation of geographical recruitment in our study, too. Moreover, the study of efficacy at a national level is of interest, as country of birth may influence cardiovascular risk in hypertensive patients [21]. Furthermore, studies of blood pressure variability and pedal edema may help better develop the subject.

Conclusion

In hypertensive patients who required combination treatment—patients previously uncontrolled on CCB monotherapy or untreated with grade 2 or 3 essential hypertension—single-pill combination indapamide SR/amlodipine reduced BP effectively, especially SBP, after 45 days. Indapamide SR/amlodipine was also safe and well tolerated.

Supporting Information

Protocol S1   Trial Protocol.
(PDF)

Checklist S1   CONSORT checklist.
(PDF)

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