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 10 018 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 [17,19] 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 inN 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%], 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 29.5/15.6 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, −2.0 mg/dL (p = 0.096); serum sodium, −0.80 mEq/L (p = 0.94); serum potassium, −0.08 mEq/L (p = 0.66); total cholesterol, +1.2 mg/dL (p = 0.50); 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].

### 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/m²) | 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.

doi:10.1371/journal.pone.0092955.t001
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 \( \Delta SBP/\Delta DBP \) 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 \( \Delta SBP/\Delta DBP \) 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/HCTZ 25 mg [25], compared with 2.52 (31.2/20.3 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: 219.2/11.1 mm Hg versus 216.4/11.4 mm Hg with CCBs, 215.6/10.8 mm Hg with ACE inhibitors, 214.8/11.4 mm Hg with beta-blockers, 213.5/11.3 with direct renin inhibitor, and 213.2/10.3 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 electrolyte 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 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].
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].
**Supporting Information**

**Protocol S1** Trial Protocol. (PDF)

**Checklist S1** CONSORT checklist. (PDF)

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